

Review

Sweat sensing in the smart wearables era: Towards integrative, multifunctional and body-compliant perspiration analysis

Christopher Legner, Upender Kalwa, Vishal Patel, Austin Chesmore, Santosh Pandey*

1050 Coover Hall, Department of Electrical and Computer Engineering, Iowa State University, Ames, Iowa, 50011, USA

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ABSTRACT

All life forms use a seamless integration of physical and chemical sensing mechanisms to enhance their performance and survival skills. To mimic the integrative sensing abilities found in nature, there is a significant interest in developing wearable devices that can smartly track the physiological and biochemical signals of the human body. Progress in wearable physical sensors has been remarkable giving rise to a number of consumer electronics products meant to measure parameters related to activity, posture, heart rate, respiration rate, and blood oxygen level. Comparatively, the progress in wearable chemical sensor development has been slower because of the inherent challenges in retrieving and processing bodily fluids. In this context, sweat provides a rich repository of biomarkers that is accessible continuously, on-the-go, and non-invasively. Here we provide a review of recent trends in the area of wearable sweat sensing with discussions on relevant topics of interest in material science, device development, sensing mechanisms, power generation, and data management. Exemplary wearable sweat sensors published in recent years are provided along with commercialization efforts in wearable sweat sensing. The review highlights the trends in multifunctional sensing platforms with flexible electronics that integrate data from both physical and biochemical sweat sensors.

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* Corresponding author.

E-mail address: pandey@iastate.edu (S. Pandey).

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1. Introduction

In 1900, the global average life expectancy was 31 years according to the World Health Organization [1]. By 2030, the average life expectancy is predicted to be more than 80 years for most of the developed world. This increase can likely be attributed to advancements in medicine and innovations in technologies to diagnose, monitor, treat, manage, and prevent diseases [1–3]. Today, personalized medicine is at the forefront of healthcare where potential risks and medical treatments are tailored according to the molecular and genetic characteristics of an individual. The premise of One Health is now accepted by society where humans, animals, and the environment are interdependent on each other. Mobile Health (or mHealth) technologies are pervasive where portable electronic devices are routinely used to collect, display, track, and communicate patient data. Medical diagnostic tools are being adapted to facilitate non-invasive and low-cost testing in the convenience of a home setting [2]. Self-managed tools are being developed to routinely monitor health parameters for early detection and timely management of diseases [3,4]. Today, smart wearable technologies are uniquely positioned to map the entire human health through integrative medicine.

Wearable physical sensors monitor various physiological parameters at real-time, including blood pressure, heart rate, respiratory rate, temperature, oxygen saturation (SpO₂), step count, and accidental falling [3,5]. Individual sensors are controlled by an embedded microprocessor that relays the gathered data wirelessly to a central processing unit. The collected data is used to track health metrics, detect anomalies in physiology, develop behavioral models, or pick up disease symptoms at an early stage. The data flow architecture can be customized and modified based on individual needs and system specifications. The passive monitoring of the physiological parameters yields valuable health information that can be communicated to medical professionals for actionable remedy [2].

In conjunction with physiological monitoring, health conditions can be assessed by wearable chemical sensors that test bodily fluids such as blood, urine, saliva, tears, and sweat [6]. Most wearable chemical sensors were originally developed to track biochemical changes in the body during physical activity, and have been adapted to diagnose clinical conditions (e.g. diabetes, hypocalcemia, liver, or renal diseases) — thus obviating the need for painful blood sampling [4,7,8]. An important advantage of wearable chemical sensors is its non-invasive feature where a bodily fluid (e.g. saliva, tears or sweat) is collected, sampled, and analyzed at the same spot to test for an analyte [9]. This is in contrast to blood tests where the bodily fluid is collected invasively (with risks of infection and injury) and processed at a separate site. There is a wealth of molecular information about the dynamics of body chemistry that can be accessed by wearable chemical sensors, increasing their potential as point-of-care devices with rapid diagnostics [7,9–13].

In recent years, sweat as a biofluid has garnered significant attention where wearable chemical sensors are being designed

specifically for sweat collection and sensing [14,15]. Compared to saliva or tears, there are fundamental advantages of using sweat for biochemical tests. There is some correlation between the levels of analytes found in sweat and blood for applications in disease diagnosis, stress observations or sports performance monitoring [5,16,17]. Techniques for collecting and testing sweat do not impede or restrict the natural movement of the wearer. As such, there is an aggressive push to commercialize sweat-based diagnostic devices that can simultaneously detect multiple analytes in a smart, low-cost, and power-efficient manner [18].

Wearable sweat sensors should possess certain attributes to make them appealing for mass adoption. Such sensors should be comfortable to wear, compact in size, flexible in shape, autonomous in operation, and provide continuous readings of the analyte [6,13,14]. It is advisable to have stability in response, reliability in measuring and sampling data, and reasonable selectivity and sensitivity with ease of calibration. The wearable device should be worn in body positions that maximize the sensing attribute and minimize skin irritation or changes from natural posture. The accuracy of the devices must be characterized in field settings to determine if the measured parameters (such as concentrations of ions in sweat) provide any clinically relevant information about the health or body activity. However, bringing new sweat diagnostics to the masses has its own set of challenges such as huge monetary costs for research and development, long timeframes for clinical tests and FDA approval, and high risks of failure in a competitive business market [4,14].

Research in the area of sweat sensing has shown a significant upward trend in the last 12 years. We surveyed articles, proceedings papers, and review papers using the Web of Science (WoS) database. To track interest in this area, we used different combinations of search keywords and visualized the data. Fig. 1a shows a significant increase in wearable sweat sensing since 2007 as the keywords “wearable”, “sweat”, and “sensor” have appeared numerous times. Papers including the keyword pair “sweat” and “sensor” have shown a significant increase over the same period; nearly doubling in the past 5 years. The keyword pair “sweat” and “monitor”, in addition to the combination of “sweat” and “microfluidic”, have also demonstrated a rising trend. Fig. 1b illustrates a word cloud generated from the keywords “wearable”, “sweat”, and “sensor”. The word cloud highlights the diverse subject areas in which the papers were published. The relative font size represents the number of papers within each subject area. While the primary area in wearable sweat sensing is related to chemistry in general (i.e. Analytical Chemistry, Electrochemistry, and Nanoscience and Nanotechnology), there is noticeable research in related areas of system design and testing (i.e. Electronic and Electrical Engineering, Instrumentation, Applied Physics, and Biomedical Engineering). The WoS search results will probably vary if other databases were used, such as Google Scholar, SCOPUS, or PubMed.

In this paper, our objective is to review the recent research in the area of wearable sweat sensing. Section 2 provides a comparison of sweat with other bodily fluids (i.e. blood, saliva, tears, urine,

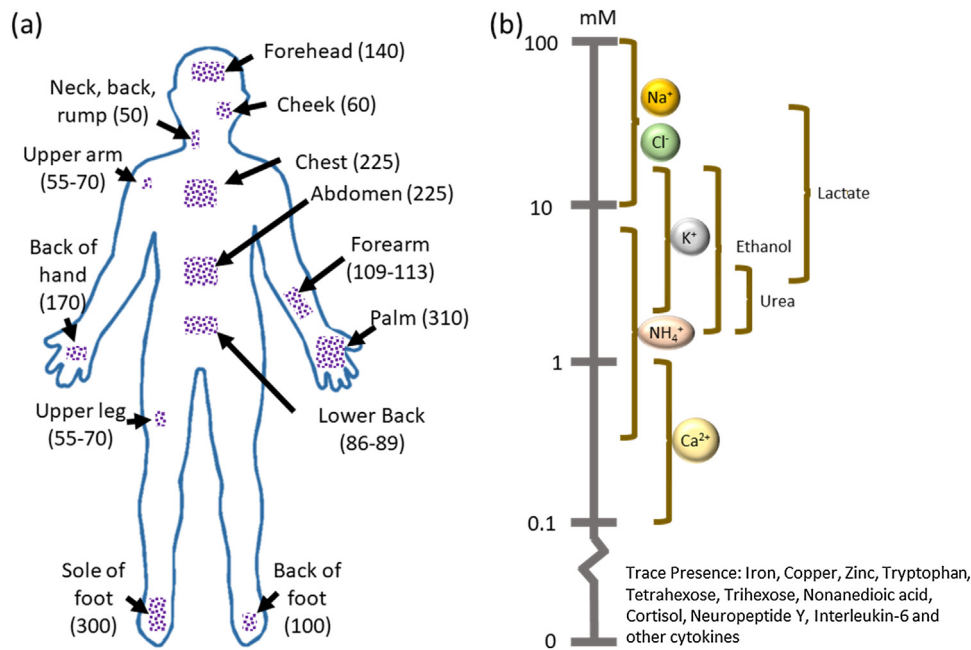


Fig. 2. Sweat as a bodily fluid. (a) Illustration of the average sweat gland density on various regions of the body in (glands/cm²) [47,52]. (b) Scale showing the approximate range of concentrations reported for different sweat analytes [16,38,41,42,50].

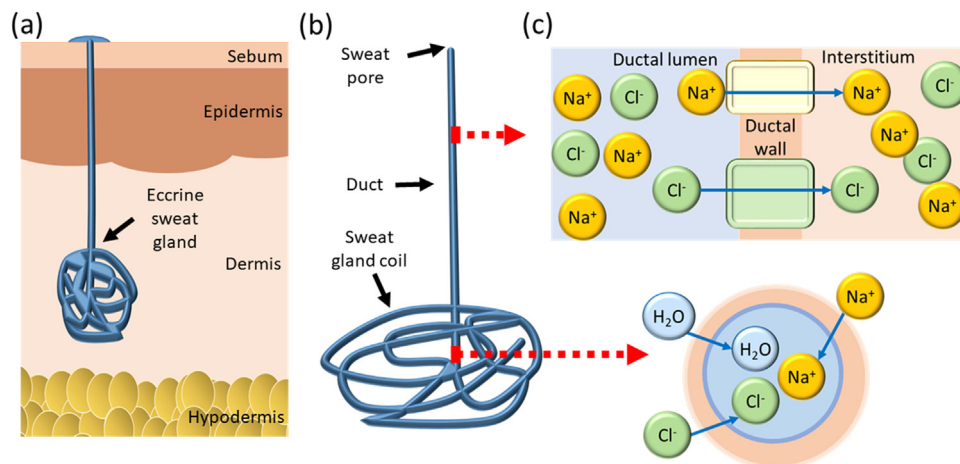


Fig. 3. Production of sweat from eccrine sweat glands. (a) Illustration of the skin structure around a sweat gland. (b) Cartoon shows the anatomy of a sweat gland. (c) Visualization of ionic flow in the ductal and coil regions of a sweat gland.

cholinergic pathways as illustrated in Fig. 3a-b. The eccrine sweat is odorless and is composed of water mixed with products that were removed from the blood such as urea, sodium chloride, proteins, and immunoglobulins (Fig. 3c). (ii) Apocrine sweat glands are located within hair follicles and are innervated by nerves of the adrenergic pathways [53,54]. Apocrine glands are typically concentrated in the private areas of the human body and are activated by emotions or stress as they are sensitive to adrenaline. Apocrine sweat contains steroids, lipids, proteins, and pheromones and can provide important physiological insights beyond the scope of eccrine sweat.

The sweat produced by eccrine glands is particularly relevant to wearable sweat sensors [18,53]. As such, it is worthwhile to understand the anatomy of the eccrine sweat glands and the method of natural production of sweat. Each eccrine gland consists of a secretory coil and a dermal duct (Fig. 3a-b) [7,55]. The secretory coil lies within the skin's dermal layer and draws in water to counter the osmotic gradient generated by sodium and chloride ions actively

being transported into it. The dermal duct carries the fluid through the dermis and to the surface of the epidermis by hydrostatic pressure where the sweat is excreted. Throughout this transport process, various chemical species (hormones, ions, metabolites, acids, small proteins and peptides) begin to enter the sweat through the dermal duct and secretory coil (Fig. 3c). It is hypothesized that many of the chemical species found in sweat are the byproduct of active or passive transport from the neighboring interstitial fluid or blood vessels. This would explain the commonalities in the analytes found in sweat, interstitial fluid, and blood as shown in Table 1.

3. Key application areas and methods of sweat production

The critical biomarkers for sweat sensing being pursued in high-performance sports and disease diagnostics are those generally related to ions in most human physiological processes. Sweat provides a rich repository of important biomarkers within the body. In general, human sweat contains electrolytes (e.g. sodium, potas-

Table 2

List of the key analytes in human sweat and associated health conditions due to their deficiencies.

Analyte	Health Condition	References
Lactate	Shift from aerobic to anaerobic metabolic conditions	[9,11,59,60]
pH	Pathogenesis of skin diseases, wound healing	[8,12,57,66,67,68]
Sodium	Dehydration, Cystic fibrosis	[2,16,21,38,43,44,45,57,58,65]
Chloride	Dehydration, Cystic fibrosis	[2,9,16,38,48,58,65]
Ammonia	Shift from aerobic to anaerobic metabolic conditions	[9,33]
Glucose	Diabetes	[5,9,10,61,62]
Ethanol	Inebriation	[9,25,39,40]
Urea/Uric Acid	Renal dysfunction	[36,37,64]
Creatinine	Renal dysfunction	[36,37,64]
Cortisol	Stress	[20,63]
Iron, Copper	Sports anemia	[16]

sium, chloride, magnesium, calcium), organic compounds (e.g. such as urea, lactate, ammonia, ethanol), metabolites, and trace compounds (e.g. iron, zinc, tryptophan, interleukin 6) [12,47,56]. The range of concentrations of different sweat analytes is illustrated in Fig. 2b. Table 2 lists the key sweat analytes and their closely associated health conditions.

3.1. Wearable sweat sensing applications

One application area for wearable sweat sensors is fitness tracking and health monitoring of athletes during high-performance sports. Sodium is the most prevalent electrolyte in human sweat, and is essential for the regulation of osmotic pressure, water balance, and pH. Sodium is an important biomarker for electrolyte imbalance, especially for athletes undergoing prolonged exercise or people exposed to hot and humid environments [2,16,21,38,41,43–45,57,58]. Sodium and chloride levels are also indicators of dehydration during the physical activities of athletes [9,51], while ammonium levels are related to extreme fatigue conditions [9,33]. Having a real-time readout of the physiological hydration levels will help to properly manage the electrolyte balance. Increased presence of lactate in sweat has been associated in a shift from aerobic to anaerobic metabolic conditions and is often produced during exercise [9,11,59,60].

The other application area for wearable sweat sensors is disease diagnostics and healthcare monitoring. Glucose and cortisol monitoring have been a major focus for sweat sensing research with hopes to offer less painful alternatives to repeated blood testing [5,7,9,10,20,61–63]. Blood glucose is a critical parameter to monitor blood sugar imbalances in diabetes (such as hypoglycemia and hyperglycemia) and has been measured by sweat analysis [5]. The monitoring of pH at a local site helps in the management of wound healing, infections, and metabolic alkalosis [57]. In addition, sweat is a means by which the body tries to excrete toxic chemicals (heavy metals [16], alcohol [9,25,39,40], urea and creatinine [36,37,64]). Sweat sensing has been clinically applied to test metabolites for illicit drugs (cocaine, opioids) with potential for diagnosis of diseases such as cystic fibrosis in newborns and infants [2,16,38,58]. In cystic fibrosis, there are genetic mutations leading to defective or absent chloride ion channels and elevated concentrations of sodium and chloride ions in the secreted sweat [58,65].

3.2. Methods of sweat production

One of the hurdles in the area of sweat sensing is the limited amount of sweat generated in sedentary individuals (e.g. physically challenged adults or newborns) and the lack of proper techniques

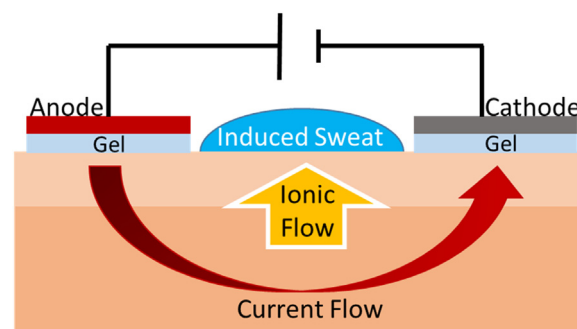


Fig. 4. Basic principle for iontophoresis. A voltage gradient is applied between the electrodes that produces a current flow below the surface of the skin. An ionic flow is established where molecules are transported through the epidermis using electroosmosis and electrophoresis. Iontophoresis is commonly used to transport pilocarpine molecules into the skin and stimulate sweat secretion.

for stimulated sweat production [65]. For accurate and stable read-out, a sweat sampling volume of around 10–200 μL would be ideal assuming that the average sweating rate of the whole body is $0.72 \pm 0.13 \text{ mg cm}^{-2} \text{ min}^{-1}$ [56]. There are two main methods of inducing sweat for sample generation: passive mechanisms (e.g. physical exercise, foot bath, sauna) and electrical stimulation (e.g. iontophoresis). Sweat collection is enabled by absorption in macroscale materials (e.g. gauze, pads, wicking fabric) or by routing the produced sweat through microscale ducts into reservoirs for sample storage and analysis.

Sweat production can be triggered passively by physical exercise (e.g. running, cycling, skipping ropes, Burpee test) or thermal stimuli (e.g. sauna, foot bath) [5,46,69]. The excreted sweat can then be collected by whole body-wash, sweat-wicking fabric, or gauze/absorbent pads (e.g. made from propylene). Here the sweat rate is typically estimated from the weight difference of clothing or pads between pre- and post-exercise. Commercial sweat collecting devices are available to directly channel the sweat produced from the skin into encapsulated chambers. An example is the MacroductTM sweat collector (ELITechGroup Biomedical Systems, UT, USA) that has a circular plastic capsule to guide the sweat from the skin surface by hydraulic pressure into a micro-bore tubing spiral [70]. The MacroductTM sweat collector needs to be firmly affixed to the skin with a good seal to avoid any leakage of fluids. Attempts have been made to develop sweat collectors in polydimethylsiloxane (PDMS) where sweat is collected by a small hole in the polymer and attached tubing [19,71]. The PDMS sweat collector was packaged as a wristwatch and interfaced with circuitry for wireless measurement of sweat conductivity. Recently, PDMS sweat collectors have been integrated with on-chip electrochemical and impedance sensing to measure the dynamics of local sweat rate and sweat contents [72]. For proper characterization, the sweat volume and sweat rate from PDMS sweat collectors are generally compared with those obtained from standardized tests (e.g. Macroduct or absorbent pads).

Sweat production can also be induced locally by means of iontophoresis [7,39]. Iontophoresis is a widely used technique to stimulate a local site on the skin for sweat generation [58]. Cryogel layers are used as the drug sorbent material where they are soaked with 1% pilocarpine nitrate (at the anode) or sodium nitrate (at the cathode). By applying an electrical current between the iontophoretic electrodes, the stimulating agonists (i.e. pilocarpine drug molecules) are delivered to the sweat glands at the anode electrode as depicted in Fig. 4. Thereafter sweat is produced but methods to collect and transport sufficient sample volumes after iontophoresis are not well established. As an example, an iontophoretic current (0.6 mA) may be injected from a standard current source (i.e. Texas Instrument LM 334) for a period of 5 min

to induce sweat production [39]. Conventional techniques of iontophoresis are prone to corrosion of electrodes and skin discomfort or irritation to the individual. Even with the known disadvantages, sweat samples extracted using iontophoresis have been analyzed for several studies such as to monitor the sweat chloride levels for cystic fibrosis [58,73], sweat ethanol concentrations for sobriety tests [25,39,40], and to measure sweat glucose levels in diabetic patients [10,61,62]. It has been shown that the biomarker levels detected in the sweat correlated closely to those monitored in the blood [5,16,17]. Barring the skin discomfort, the convenience of collecting sweat for sampling makes iontophoresis an ideal candidate for non-invasive wearable implementation.

3.3. Fundamental challenges with sweat as a sensing fluid

There are challenges in using sweat for detecting analytes [62]. The sweating rates of skin glands and sweat volume can vary at different regions of the body and among different individuals, besides depending on the nature and duration of physical exercise [41,52,56]. In extreme cases, some individuals lose their ability to secrete sweat (i.e. anhidrosis) or produce excessive amounts of sweat (i.e. hyperhidrosis). Sufficient volume of fresh sweat (10–20 μL), along with disposal of old sweat, is important to realize continuous sweat sensing devices [72]. The environment, especially conditions of high humidity and temperature, can affect the sweat rate of an individual which is around 1 to 20 nL/min/gland [41,72]. It is unclear exactly how the cellular machinery operates to change the sweat output in response to heat or exercise [67]. Significant electrolyte loss can occur due to exercise intensity, exposure to heat stress or hydration status of the body [41]. The dietary patterns and consumed foods can alter sweat composition [12,47,52]. For example, some food and drinks are known to be high in sodium (pretzels, salted nuts, canned meat, and carbonated drinks), potassium (bananas, leafy greens, and oranges), or calcium (milk, yogurt, cheese, and sardines). It is unclear how sweat composition changes post-meal in individuals with varied levels of metabolism. In addition, it is difficult to predict the relationships between the biomarkers and vital signs, and how their concentrations change in time throughout the course of dehydration. The correlation between levels of biomarkers in sweat and blood need to be studied closely taking into account the different factors in play. In this context, ethanol is a strong validation marker with 1:1 correlation between sweat and blood due to its small lipophilic nature. It was shown that sweat alcohol levels have a distinct lag time (6.5 min) from the blood alcohol level which can be attributed to the complex partitioning of ethanol in human tissues [74]. While the concentrations of most sweat analytes are proportional to the sweat rate, the concentrations of other sweat analytes (e.g. lactate) are difficult to estimate and relate to their levels in blood. This may be due to factors such as differential absorption and penetration of molecules through the blood-skin barrier, uncontrolled stimulation of sweat ducts and glands, and changing vascular permeability into the skin [75]. The concentrations of metals (iron, zinc, and copper) in sweat, plasma, and blood may show great variability among different individuals and a consistent prediction of metal deficiencies over time is difficult [16]. As such, continuous correlation of sweat- and blood-related data has remained a fundamental challenge in sweat sensing, particularly for high-value analytes (i.e. hormones, cytokines, and proteins) [74].

4. Materials for sweat sensing devices

The design concepts of traditional chemical sensors may not be apt for making their wearable counterparts, particularly with respect to size, rigidity, and self-healing [11]. For example, tradi-

tional chemical sensors are bulky and voluminous while wearable sensors need to be light-weight, small-sized and portable. Traditional chemical sensors are fabricated on rigid substrates which are not suitable for mounting on the human body [76–78]. Today, the design and fabrication protocols for wearables are largely inspired by the field of electrochemistry, organic electronics, solar cells, and large area flexible electronics [11,79–81]. Fabrication processes are tailored towards all-solid-state ion-selective electrodes, polymers, and membranes where the wearable device community is constantly seeking key drivers for low-cost, miniaturization, reliability, small sample volumes, and simplicity of design [66].

The choice of materials and electrochemical sensing methods is generally dependent on the target biomarker in the sweat, especially its molecular properties and concentration range [82,83]. Other considerations include the system cost, application requirements, and timeframe for sampling-to-detection [66]. The sweat electrolytes (such as sodium, chloride, potassium, calcium) are often in the millimolar range and are detected using ion-selective electrodes (ISEs) and potentiometry [81,84,85]. On the other hand, metabolites (such as glucose and lactate) are often in the sub-milli to micromolar range and are detected using enzymatic reactions and amperometry [19,86]. Detection of biomarker molecules in the sub-micromolar range is challenging because of sensor sensitivity and interfering chemical species in sweat.

4.1. Flexible substrates and electrodes

Wearable sweat sensors employ electrode systems for the detection of ions on the skin such as chloride, glucose, lactose, and hydronium ions. For amperometry and voltammetry, the basic electrode system in the sweat sensing electrochemical cell involves the use of flexible electrodes (working, reference, and counter electrodes). The sweat chloride ions are detected using Ag/AgCl electrodes while pH detection is accomplished by polyaniline or iridium oxide coatings [66]. For preparing chloride-sensitive Ag/AgCl electrodes, FeCl_3 solution is injected on top of Ag electrode [65]. The glucose and lactose in sweat can be detected using a classic two-electrode system where Ag/AgCl is used as both the reference and counter electrodes. For glucose detection, a mixture of glucose oxidase/chitosan/carbon nanotube is drop-cast on Au electrodes coated with Prussian blue mediator layer. Similarly for lactate sensing, a mixture of lactate oxidase/chitosan/carbon nanotube is drop-cast on Prussian blue coated Au electrodes [87]. For alcohol testing, the alcohol oxidase (AOx) enzyme is mixed with bovine serum albumin stabilizer and chitosan solution, and drop-cast on a conductive carbon ink electrode [39].

For designing the flexible electrodes to be used in sweat sensors, conductive tracks (made of Au, Ag, Pt, graphite, or carbon nanotubes) are fabricated on flexible, polymeric substrates (e.g. parylene, polypyrrole, polydimethylsiloxane (PDMS), polyethylene naphthalate (PEN), and polyethylene terephthalate (PET), or Kapton) [35,66,67,88,89]. PET is the most common example of flexible, polymeric substrates for wearable sweat sensors. The conductive substrates can also be directly integrated into conventional non-conductive materials such as paper, plastic, rubber, and cotton yarns [77,79,90]. Some of the popular conducting polymers include poly(3,4-ethylenedioxythiophene) (PEDOT:PSS), polyaniline (PANI), polypyrrole (PP), polythiophene (PT), polyphenylene sulfide (PPS), and poly(3-octylthiophene) (POT) [91]. Among these, PEDOT:PSS is the most widely studied conducting polymer as an ion-to-electron transducer for sweat analytes as it has very good stability and sensitivity characteristics [87,92,93].

Flexible electrodes for sweat sensors are generally fabricated by screen-printing and photolithography, even though other methods have been explored such as dip-coating, sputtering, and e-beam evaporation [45,66,90,94,95]. Photolithography provides

the advantage of high-resolution patterning, but requires expensive instruments and multiple intermediate steps of light exposure and rinsing [96]. Screen-printing, which has been exploited in the textile industry, is adaptable for mass production and consumes lower reagent volumes [83]. The reference electrode material is often a conducting polymer, carbon material, or Ag/AgCl which is then covered with a polymeric reference membrane and doped with lipophilic ions. The saturated concentration of lipophilic ions in the membrane is preserved by using polyacrylate or polyvinyl butyral (PVB). A thin layer of paralyne C can be deposited over the electrodes for proper insulation [87]. For wearable sweat sensing applications, PVB-based reference electrodes are widely used because of their high stability in generating the interfacial potential, along with the ease of fabrication and compatibility with printing techniques [97,98]. Fabricated reference electrodes need to maintain a constant voltage with minimal drifts (on the order of $500 \mu\text{V h}^{-1}$) because of chemical fluctuations in the sample or biofouling from materials or electrolytes [98].

4.2. Ion-selective membranes and colorimetric assays

Ion-selective membrane (ISM) have been used for potentiometric sensing of specific ions in the sweat such as Na^+ , K^+ , and Ca^{2+} . The membrane is deposited on top of a conductive polymer which can be drop-cast on a metal substrate (such as gold, silver, or glassy carbon) or electro-polymerized from the monomer [66,81]. Cocktails of specific ions are prepared and drop-cast on top of their corresponding electrodes, along with reference solution on top of the Ag/AgCl reference electrode. After drying overnight and proper conditioning to avoid drift, the potentiometric electrodes are ready for use. In addition, it is necessary to ensure there is sufficient physical adhesion between the ion-selective membrane and the substrate. Otherwise a water layer may form between the membrane and substrate that will act as a fluid reservoir and alter the equilibrium conditions [84,99]. By adding polyurethane (PU) into the plasticizer of the ion-selective membrane (weight ratio of 1:1 PU/plasticizer), there is an increase in the membrane robustness and adherence when compared to traditional membranes having polyvinyl-chloride (PVC) in the plasticizer (weight ratio of 1:2 PVC/plasticizer) [81,85,100]. Other materials to be inserted in the ion-selective membranes are being explored such as polyacrylates, ionic liquids, polystyrenes, grafted carboranes, and semifluorinated polymers [101,102]. Thus far, PU is the best candidate as it provides high adherence to the substrates, acceptable biocompatibility with negligible biofouling, and mechanical stability throughout a range of motions (such as bending, stretching, twisting, poking or rubbing) [66,85].

Besides the use of ISMs for potentiometric sweat sensing, colorimetric assays have been constructed on flexible elastomers for a direct readout of color change in the presence of desired sweat analytes. A master mold is made by patterning the desired photoreactant on a silicon wafer. The elastomer (such as PDMS) is spin-coated on the master mold and cured to form microchannels and reservoirs. Color reference markers are incorporated within polyester films and attached to the PDMS device, along with medical grade acrylate adhesive for adhesion of the device to the skin [64]. Alternatively, the chromogenic reagents can be spotted on a filter paper and put inside the microfluidic reservoirs for colorimetric tests [19]. A number of low-cost colorimetric kits are commercially available to detect the common sweat analytes. Glucose is detected by a mixture of glucose oxidase, trehalose, horseradish peroxidase, and potassium iodide in sodium citrate buffer. Similarly, levels of lactate and chloride are detected by the D-Lactate Assay Kit and Chloride Assay Kit, respectively. The sweat pH can be detected by the universal pH indicator. Cobalt chloride dissolved in PHEMA has been used as a colorimetric marker for the pres-

ence of water, and in turn the sweat flow rate [19]. Besides PDMS, poly(styrene-isoprene-styrene) (SIS) elastomer has been used to develop an underwater, skin-compatible microfluidic device. The SIS elastomer is suitable for aquatic environments because of its hydrophobicity, optical transparency, high elasticity, and very low rates of water penetration. A color reference dial has been incorporated within the SIS layer for direct colorimetric readout of sweat chloride levels [69].

5. Device configurations

Device configurations for wearable sweat sensors are generally motivated by the ability to create flexible platforms that can conform to the shape of the body part without impeding the natural activity of the user. Some methods of sweat collection from the skin as reported in published literature are illustrated in Fig. 5. Such devices may be worn in body positions (forehead, chest, back, wrist or sole) where there is adequate sweat production. Here we show examples of a wristwatch sweat collector (Fig. 5a), a wrist sweat-band with flexible printed electrodes (Fig. 5b), a skin-mounted band with superwetttable reservoirs (Fig. 5c), a Macroduct™ sweat collector integrated with an arm-based calorimetric sensor, and a skin-attached, glucose-sensing strip with a wrist-based smart band (Fig. 5e). In general, the choice of the device configuration depends on several factors such as cost, weight, reusability, robustness, accessibility to sweat, time to collect sweat and sense analytes, biocompatibility, and aesthetics. Device configurations can be broadly categorized into on-skin sweat sensors (e.g. sweatbands, patches, tattoos, and skin-worn microfluidics) and near-skin sweat sensors (e.g. textiles and garments) [7,15,53,66].

5.1. On-skin wearable sweat sensors

On-skin wearable sweat sensors collect and test the sweat sample on the same spot while minimizing evaporation. Because of the proximity to the sample collection site, on-skin sweat sensors can record changes in concentration of biomarkers in substantially smaller timeframes before degradation of the sample occurs. By using the same site for sweat generation, collection, sampling, and testing, the design constraints of on-skin sweat sensors are less complex in comparison to current electrochemical assays [43,61,103]. These sensors however have risks of skin irritation and contamination from the sweat produced in neighboring areas.

Sweatbands provide a convenient platform to attach the wearable accessories (stretchable electrodes and sweat sampling cell) and dispose of them after use [21,88]. Previous sweatbands have been tightly attached to the arm, back, forehead, or wrist of an individual with integrated absorbent pads that act as sweat sampling cells [21,69,88,104]. Sweatbands have also been integrated with iontophoresis systems to actively stimulate the sweat glands and extract the sweat sample [46,61]. However, iontophoresis can lead to skin damage or skin irritation because of the applied currents or contact with agonist stimulants or hydrogels.

Epidermal patches and tattoos provide direct contact to the skin and have the ability to measure sweat parameters in any region of the body. Unlike sweatbands, epidermal patches and tattoos require much better mechanical strength, resilience, and adhesion to the skin especially under high-intensity physical activity. Recently, the concept of embedding sweat sensors within temporary tattoos has gained attention [33,43,49,105]. Here, the sensing electrodes can be directly placed on temporary tattoo paper by screen-printing techniques. The electrode-containing tattoo is then adhered to the patient's skin to monitor the profile of analytes in sweat including pH, ammonium, lactate, sodium, and skin hydration [12,33,88].

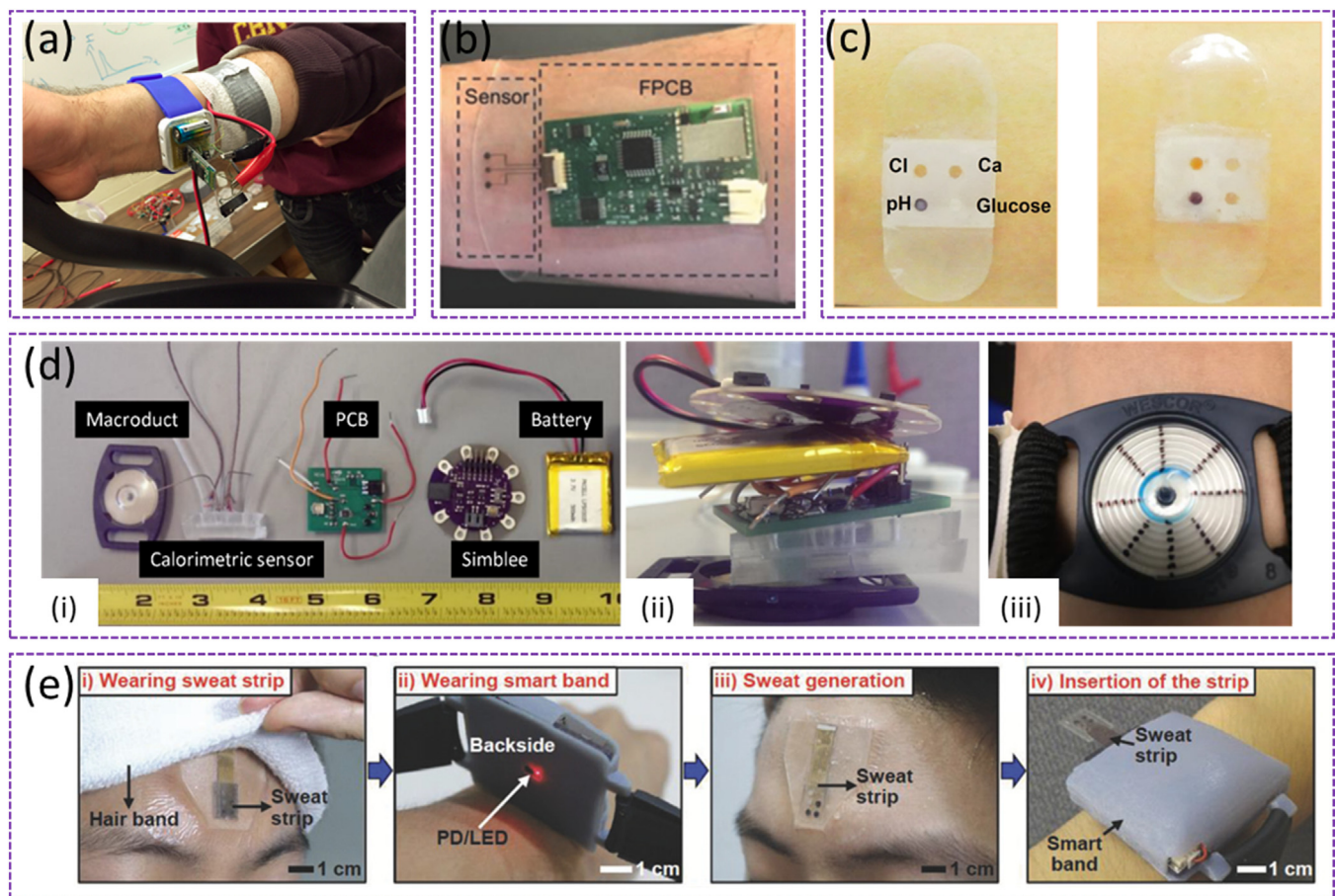


Fig. 5. Example methods of on-skin sweat sensing. (a) A wristwatch sweat collector is shown with wireless measurement of sweat conductivity on a subject during exercise. Reprinted (adapted) with permission from ref. [71]. Copyright (2016) Elsevier. (b) A wrist sweatband, called s-band, with flexible printed electrodes is shown for the *in-situ* detection of caffeine in sweat. Reprinted (adapted) with permission from ref. [46]. Copyright (2018) John Wiley and Sons. (c) A flexible, skin-mounted band with superwetttable reservoirs is shown for sweat collection and colorimetric detection of four analytes in sweat (pH, glucose, chloride, and calcium ions). Reprinted (adapted) with permission from ref. [55]. Copyright (2019) American Chemical Society. (d) The Macroduct™ sweat collector is integrated with a calorimetric sensor and worn on the arm to detect and display the sweat rate information wirelessly using a LilyPad Simblee Bluetooth board. Reprinted (adapted) with permission from ref. [70]. Copyright (2018) MDPI Sensors. Reproduced under the Creative Commons Attribution License (CC BY 4.0). (e) A sweat strip is attached to the skin of the forehead to collect the generated sweat. The sweat strip is inserted into a wrist-based smart band to measure the glucose levels in sweat. Reprinted (adapted) with permission from ref. [5]. Copyright (2018) John Wiley and Sons.

Skin-worn microfluidic patches are also directly attached onto the skin and can have multifunctional features for autonomous sweat collection, storage, and analysis. These devices typically bypass the need for on-board electronics, batteries or signal processing. A medical-grade, double-sided adhesive film is used for attachment to the skin. There are integrated microfluidic channels to automatically guide the sweat (passively by capillary forces or valves) into miniaturized reservoirs where colorimetric reagents are present for on-site chemical analysis of sweat contents. Images of colorimetric tests can be processed by custom smartphone apps, which obviates the need for on-board power consumption [104]. Water-responsive chromogenic reagents can be filled in the microfluidic channels to infer the sweat rate and volume. A magnetic loop antenna with associated near-field communication (NFC) electronics has been integrated with the skin-worn microfluidic system for interface with external devices [19].

5.2. Near-skin wearable sweat sensors

Near-skin sweat sensors constantly wick the produced sweat and transport it through fluidic channels to the electrodes; thereby avoiding issues of sweat pooling and contamination [62,102,103]. The parameters of fluidic channels for sweat transport can be optimized (such as shorter length, larger width) to increase

the flow rate, reduce contamination, and minimize sampling-to-measurement time. An example of near-skin wearable sweat sensors is within the area of textiles and garments where a variety of architectures have been employed to integrate functioning wearable sensors in a clothing matrix [66,79]. Different configurations of sensor integration into textiles have been explored, such as yarns modified into conductive substrates with sensing membranes or commercial garments directly fabricated with electrodes [105,106]. A number of moisture-wicking fabrics (Polyester or Nylon) and moisture absorbing fabrics (Tencel®, Modal, Viscose, cotton) can be adapted to collect sweat and analyze it. Techniques to alter or tailor the conventional manufacturing processes are being investigated to produce textiles integrated with sensors and electrodes [6,22]. Mass production of low-cost and highly malleable substrates (such as plastics) is well-suited for attachment to the textiles or skin for long-term monitoring of sweat physiology. As a limitation, it is unclear whether wearable sensors integrated with textiles can withstand multiple rounds of washing and drying without compromising their performance [12,13]. Otherwise, the wearable sensors can be configured to be attached or detached from the textiles with plug-ins for assembling the sensors and powering them.

For both on-skin and near-skin wearable sweat sensors, mechanical testing is generally conducted in the laboratory to eval-

Table 3

List of different sensing platforms and sensing modalities for testing analytes in sweat.

Sensing Platform	Sensing Modality	Tested Analyte	References
Cotton textiles	Amperometry, Potentiometry	β -nicotinamide adenine dinucleotide, pH, Ammonium, Potassium, Hydrogen peroxide	[79,106]
Polyimide/Lycra blend	Potentiometry	Sodium	[44]
Polyester	Potentiometry	Chloride	[73]
Gas-permeable membrane	Amperometry	Oxygen	[108]
Stamps	Voltammetry	Uric acid	[109]
Temporary tattoo	Potentiometry, Voltammetry	Lactate oxidase, pH, Ammonium, Sodium	[33,43,59,68]
Patches	Conductometry, Amperometry, Potentiometry	Sodium, Potassium, Glucose, Lactate, Chloride, pH, Humidity, Potassium, Lactate	[8,60,65,67,97]
Eyeglasses sensor	Amperometry, Potentiometry		[110]

uate the physical strength, flexibility, resilience, and durability during field experiments. Wearable sweat sensors need to provide stable and strong adhesion to the skin without causing unwanted irritation or itching even after prolonged use. To adequately conform to the skin, it is found that the substrate thickness should be around 25 μm and an elastic modulus less than 100 kPa [107]. Recently, wearable sweat sensors have incorporated a medical-grade acrylic adhesive film between the base of the device and the skin. This adhesive film has a thin geometry (25 μm thick), low modulus (17 kPa), and a much stronger adhesion (5.7 N) to skin compared to other medical-grade adhesives. Besides, flexibility and soft mechanics of the wearable sweat sensors are often desired. The most favorable set of physical characteristics are offered by PDMS sweat patches (e.g. low modulus of 145 kPa and high elasticity of up to 200% strain at breaking point). Finite element analysis (FEA) of stress and strain distributions under different mechanical loads is typically performed to understand the limits of stretching, bending, and twisting the device [19]. To test whether the wearable sweat sensor is mechanically robust for human wear, the device performance can be monitored when exposed to several cycles of 180° bending strain or stretching strain of about 27%. Further tests on mechanical deformation have been conducted by poking or creating indentations in the device to check if the structural integrity is still preserved [43].

6. Sensing modalities

Most electrochemical sensing devices base their measurements in some form of amperometry, potentiometry, voltammetry or colorimetric techniques [7,11,66]. Table 3 lists a number of sensing platforms based on their sensing modalities and tested analytes in sweat. Some methods of on-board fabricated electrodes and sensing modalities to identify sweat analytes are depicted in Fig. 6. Here we show examples of integrated electrodes for amperometric sensing of alcohol (Fig. 6a), cortisol-binding DNA aptamers for colorimetric readout (Fig. 6b), screen printed Ag/AgCl electrodes for amperometric sensing of chloride ions (Fig. 6c), ion-selective field-effect transistor (ISFET) for pH sensing (Fig. 6d), and colorimetric assays with soft microfluidics and capillary bursting valves for detecting specific enzymatic reactions (Fig. 6e).

6.1. Potentiometry, amperometry, voltammetry, and colorimetry

Potentiometry measures the potential between a sensing and reference electrode to determine changes in ionic concentration within a solution [66,81]. This method is ion specific and the ionic concentration is indirectly measured through the electrochemical activity. Specific ion-selective membranes have to be designed to target and separate specific ions from the rest of the sample [7].

Amperometric sensors monitor the current produced by oxidation or reduction reactions between electroactive species under a constant potential [4,86,106]. The produced current change is proportional to the concentrations of the electroactive species [5]. Amperometric sensors often use selective enzymes to target the specific chemical reaction of interest. For example, lactate oxidase and glucose oxidase are enzymes that are typically used for the measurement of lactate and glucose concentrations in biofluids, respectively [11]. Similar to potentiometry, the measurement technique is simple and little post-processing is required to associate the current signal to the analyte concentration [7]. A pre-stabilization step is often recommended prior to current recording where all electrodes are shorted to a conductive film. This helps to compensate for the potential difference between different electrode materials and reduce the time lag for current saturation [5]. Amperometric sensing can have difficulty measuring trace species in concentrations below the μM range.

Voltammetric sensors take a voltage scan between a reference and sensing electrode as a function of time. Unlike potentiometry or amperometry, voltammetry can measure multiple analytes simultaneously because the measurement is related to the redox potentials of the different chemical species. However, the act of sweeping the voltage over a certain range can induce background electrochemical reactions interfering with some measurements [7].

Colorimetric sensors expose the samples to different chemical reagents pre-designed to exhibit color changes in the presence of specific chemical analytes (Fig. 6e) [12,64,76,111]. In general, colorimetric tests are more qualitative than quantitative as these tests often are used to detect the presence of chemical species rather than quantify their concentrations. Image processing tools have been employed to correlate color differences with chemical concentration levels [76,111–113].

6.2. Performance matrix of wearable sweat sensors

The device operation and performance is generally evaluated in terms of stability, limit of detection, response time, and calibration [13–15,66].

The stability of the reagents used in sweat sensors degrade over time, especially with fluctuations in temperature, humidity, pressure, and pH. After such exposure, the denatured compounds can slowly lead to drifts from the optimal performance metrics, thereby compromising the stability of the devices [15]. In addition, the limit of detection is an important performance parameter because the concentrations of analytes in sweat are usually much lower than those in blood (e.g. cortisol in Fig. 6b). This is also true for other bodily fluids retrieved non-invasively. Being able to detect low concentrations is particularly relevant for applications where sweat sample is used to detect metabolites, hormones, trace metals, toxic gases, and contraband drugs [13,16,46].

The response time of wearable sweat sensors is chosen to be short (of few minutes) so that the analytes are continuously detected and displayed to the user within a reasonable time frame. Enzymatic sensors that rely on catalytic reactions are considerably fast and have a short response time, while bioaffinity-based sensors that rely on chemical binding have a slow response time (> 15 min) [13,85,98,114]. The use of biological receptors could be prone to degradation over time, and alternatives in synthetic probes

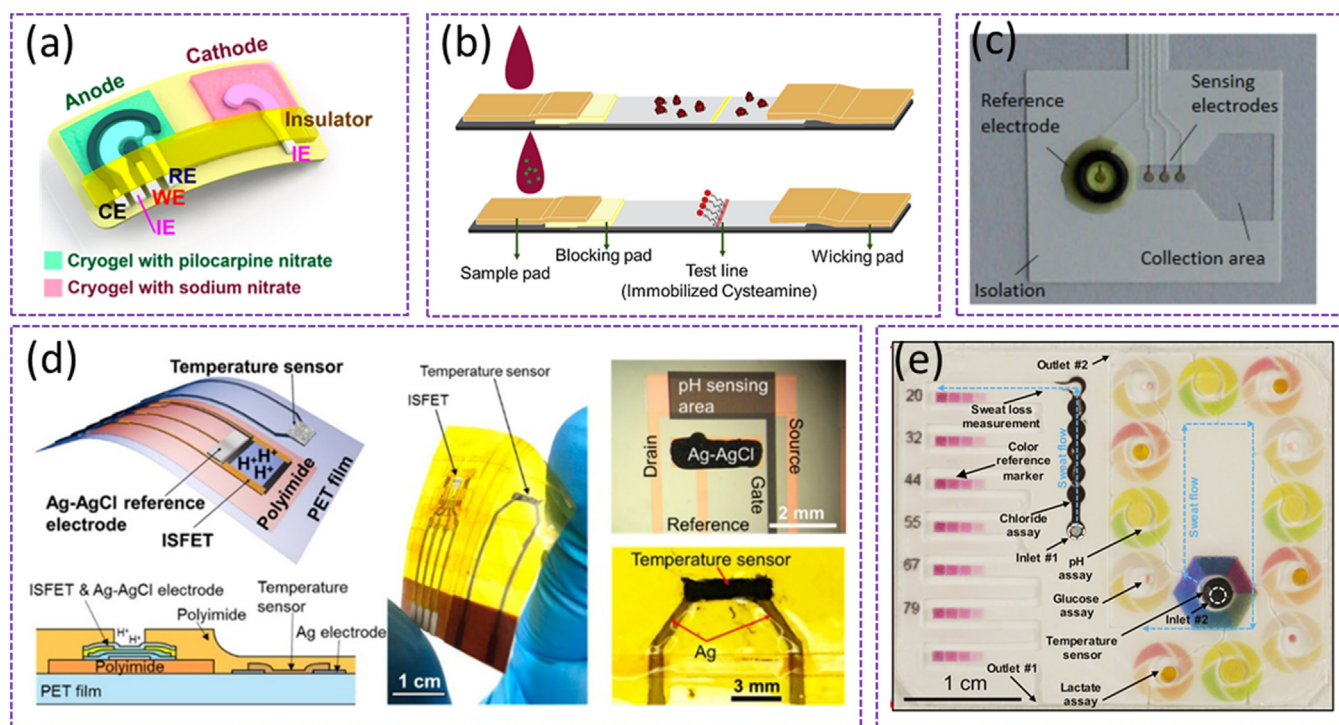


Fig. 6. Examples of different sensing modalities for sweat analysis. (a) A flexible alcohol monitoring device is shown with integrated electrodes for constant-current iontophoresis and amperometric sensing. The drug pilocarpine is loaded in the cryogel at the anode that induces sweat production. Amperometric sensing is accomplished by using alcohol oxidase enzymatic reactions. All electrodes are fabricated by screen printing. Reprinted (adapted) with permission from ref. [39]. Copyright (2016) American Chemical Society. (b) A lateral flow assay is shown for the colorimetric detection of cortisol, a stress biomarker. The assays consist of a sample pad, blocking pad, test line, and wicking pad. Cortisol-binding DNA aptamers are conjugated with gold nanoparticles (AuNPs). In the presence of cortisol, the aptamers are dissociated from the surface of AuNPs which eventually aggregate in the test line as a clear red line. Reprinted (adapted) with permission from ref. [63]. Copyright (2019) Elsevier. (c) A sweat chloride patch is shown with three identical sensing electrodes and one reference electrode. The Ag/AgCl electrodes are screen-printed on a flexible polyethylene terephthalate (PET) sheet. The temporal changes in the electrode potential are used to estimate the sweat chloride concentrations with a chloride sensitivity of 56 mV/decade. Reprinted (adapted) with permission from ref. [48]. Copyright (2015) Elsevier. (d) A flexible, wearable platform is shown that incorporates sensors for the real-time measurements of sweat pH and skin temperature. An ion-selective field-effect transistor (ISFET) is used as the pH sensor with Ag/AgCl as the reference electrode. All the sensors and electrodes are fully integrated on a polyethylene terephthalate (PET) film and insulated with polyimide. Reprinted (adapted) with permission from ref. [128]. Copyright (2017) American Chemical Society. (e) A skin-compatible device is fabricated in soft microfluidics and has multiple reservoirs accessed by capillary bursting valves. The sweat pH, temperature, and chloride are determined by chemical reactions, while glucose and lactate are detected by enzymatic reactions. The digital images produced from the colorimetric assays are processed by a smartphone. Reprinted (adapted) with permission from ref. [82]. Copyright (2019) American Chemical Society (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

could be investigated that mimic the specificity and bioaffinity of biological counterparts (Fig. 6b) [112,113]. As such, enzymatic sensors (Fig. 6a) are best suited for continuous monitoring of analyte concentrations in sweat. But there are issues with washing and cleaning the sensors for repeated, long-term readings as most sensing protocols require multiple steps for calibration and resetting [6,12].

There is increasing interest in calibration-free sweat sensors that provide uninterrupted service to the user. Today most sensors (physical and chemical) need some sort of calibration before use with resetting or recalibrating the sensors at regular intervals (Fig. 6c-d) [114,115]. Otherwise, there may be drifts in the signal that can introduce error during data acquisition. However, it is difficult to fathom exactly how calibration-free sensors could be realized that literally require no calibration throughout the sensor's lifetime [14].

7. Electronics, power generation, and data management

7.1. Integrated electronics with power generation and storage

Typically, the electronics for a wearable device perform signal transduction (where frontend sensors convert chemical signals to electrical equivalents), signal conditioning (where amplifiers and low-pass filters accentuate the desired signal), signal pro-

cessing (where a microcontroller with analog to digital converters calibrate and control the signal flow), and wireless communication to transmit the data to a remote computing device for analysis and visualization [5,7,14]. Fig. 7 shows some methods of integrating the electronics with sensing devices for the automated readout of sweat parameters. Here we show examples of a wristwatch sweat conductivity sensor with on-board oscillator, microcontroller, and Bluetooth module (Fig. 7a), a smart band with a printed circuit board (PCB) having physical/chemical sensors and a Bluetooth module (Fig. 7b), and a wearable sweatband with PCB having a microcontroller, data converters, and Bluetooth transceiver (Fig. 7c).

Reducing power consumption is a major requirement for wearable devices as they need to operate continuously for extended periods of time. Power efficiency will become all-the-more critical as we increase the number of sensors on the wearable platform; each sensor aimed at gathering data on multiple parameters at near real-time sampling rates [13,116]. The electronics in the wearable sensor platforms are best powered by wearable or portable energy resources that can be integrated for on-the-body mobile applications. Current trends in wearable energy resources fall in the two broad categories of lithium-ion batteries and energy harvesting devices [80,117–119].

Lithium-ion batteries are considered to have an impressively long working life with fast charging and recharging features [13].

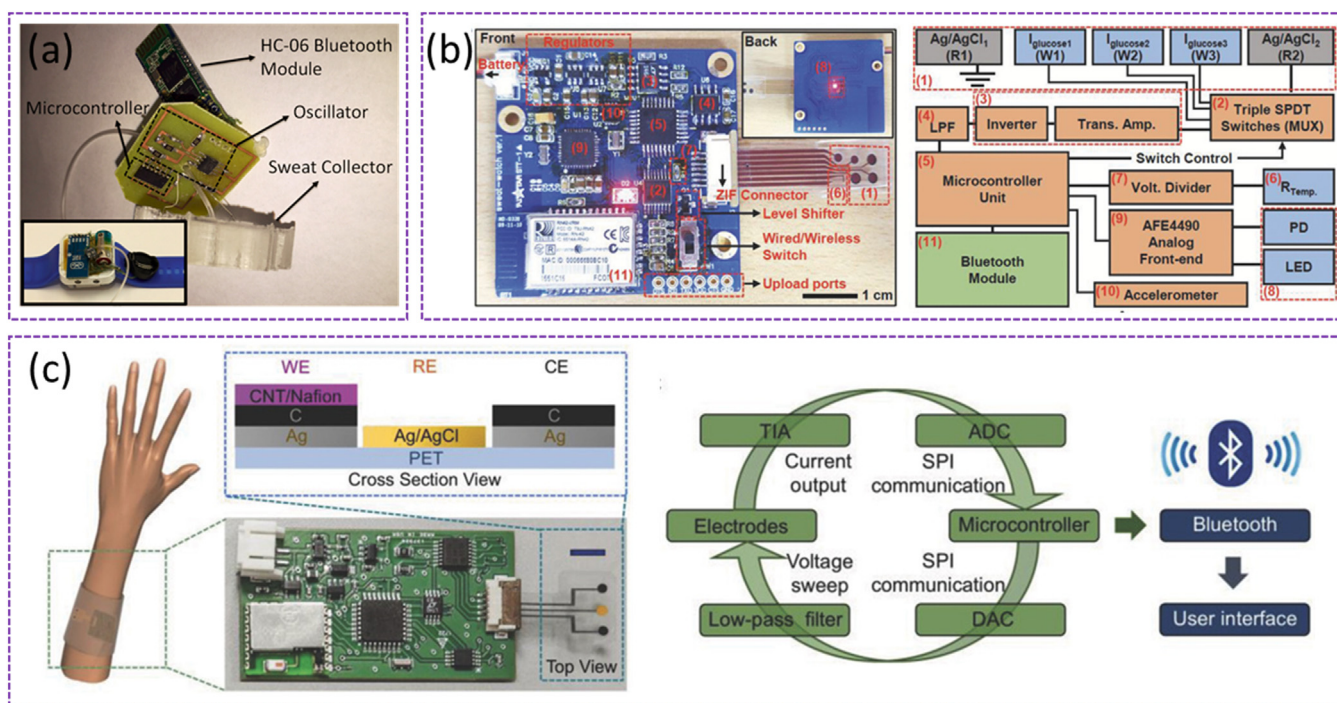


Fig. 7. Examples of the interfacing electronics for sweat sensing applications. (a) A wristwatch model has a wireless sweat conductivity sensor controlled by an oscillator, microcontroller, and Bluetooth module. Reprinted (adapted) with permission from ref. [71]. Copyright (2016) Elsevier. (b) A smart band is developed with a printed circuit board (PCB) to read data from electrochemical and physiological sensors. The PCB has a microcontroller, transimpedance amplifiers, low-pass filters (LPF), multiplexers (MUX), pulse oximeter, heart rate sensor, accelerometers, and Bluetooth module. The MUX controls the three working electrodes and one Ag/AgCl reference electrode. The other Ag/AgCl electrode is grounded. Reprinted (adapted) with permission from ref. [5]. Copyright (2018) John Wiley and Sons. (c) A wearable sweatband with flexible electrodes detects caffeine using differential pulse voltammetry. The PCB has a microcontroller, analog-to-digital converter, digital-to-analog converter, low-pass filter, and Bluetooth transceiver. Communication between microcontroller and data converters uses SPI protocol while Bluetooth communication uses the Universal Asynchronous Receiver/Transmitter (UART) protocol. Reprinted (adapted) with permission from ref. [46]. Copyright (2018) John Wiley and Sons.

As an example, the most common lithium ion coin cell battery is the CR2032 having an amperage of 225 mAh, operating voltage of 3 V, and weight of 2.9 gm (wattage: 675 mWh). Assuming a power consumption of 10 μ W/bit for the sensor data, approximately 22,500 bits can be transferred in a 3-h period. However, the form factor of lithium-ion batteries is incompatible with the needs of the wearable industry. They are difficult to scale to smaller sizes while maintaining their performance because reducing its physical size lowers the energy stored in the battery. They are often much heavier than the wearable sensors and made from rigid, toxic materials that do not conform to the body shape. As such, there have been efforts to incorporate the best features of lithium-ion batteries in wearable and body-compliant formats; thereby selecting the best of both worlds. Batteries have been built on flexible substrates such as elastomers, paper, and textiles. For example, a flexible and stretchable battery has been demonstrated by putting the battery components of a conventional battery on to an elastomer substrate [119]. To minimize the risks of swelling and blowing up in overheated lithium-ion batteries, protective coatings have been built for these batteries to turn off the power unit in case of overheating [120].

Energy harvesting devices are being investigated that scavenge energy from a plurality of sources such as kinetic energy, friction, heat, chemical reactions, or sunlight [13]. The primary goal is to find a suitable power alternative to lithium-ion batteries in a wearable format with a long life, rapid charging rate, and adequate biocompatibility of materials used. Unfortunately, several small-scale energy harvesting devices (e.g. piezoelectric crystals, thermoelectric generators, micro wind turbines, photovoltaics) cannot be scaled and incorporated in wearables. Most of these energy sources (e.g. solar cells, biofuel cells) struggle with a short working life with

long charging times and fluctuations in energy efficiency. For example, solar cells and photovoltaics require a large surface area to capture most of the incident solar energy, suffering from considerably low efficiency when the sunlight is not incident normal to its surface (e.g. on a three-dimensional skin surface or during body movement). Similar to solar cells, biofuel cells are low efficiency, have short working lives, and struggle to perform or survive in harsh climates and environmental conditions [117]. The leakage of chemical reagents (e.g. silicon tetrachloride, cadmium compounds, hexafluoroethane, lead, microbes, oxido-reductase enzymes) during the leaching or degradation of solar or biofuel cells is a concern for mass adoption because these chemicals can be caustic to the human skin. Recent trends in realizing efficient and low-cost solar cells include the use of perovskites and stretchable or flexible materials with conventional solar cell topologies [80]. In the category of biofuel cells for wearable devices, there are reports of a highly stretchable glucose biofuel cell, textile-based stretchable biofuel cells, stabilizing agents for enzymes used in chemical reactions, and rechargeable biofuel cells [117]. The area of soft and origami-based robotics provides promising ideas for self-powered sensors and actuators that can be adopted in integrated wearable devices [96,111,121,122].

Mobile power storage has garnered tremendous interest to address the energy demands in consumer electronics [13]. For instance, supercapacitors are gaining much attention as high-capacity capacitors which store much higher energy per unit volume than available batteries or electrolytic capacitors. They can tolerate many more charging/discharging cycles (100 k to 1000 k) and accept/deliver charges at a much faster rate. The energy harvesting devices can be integrated with wearable supercapacitors to store the scavenged power. The supercapacitors would then

provide the stored energy to the wearable sensors as needed. The option of having a constant, mobile energy source for powering their wearable sensor electronics is appealing to the end user. As such, the goal here is to realize supercapacitors with high volumetric and gravimetric performances, high mechanical resilience, low internal resistance, reduced discharge rate, and reasonable cost [118]. To date, lithium-ion supercapacitors offer the highest gravimetric specific energy of around 15 Wh/kg or 54 kJ/kg. Studies in material science and chemistry are helping us answer questions on how to realize robust supercapacitors with the most appropriate materials (electrolytes, electrode materials, binder, and additives), packaging methods, and electrical characteristics (shelf-life, working life time, charging time, leakage current, series resistance, degradation with time). In this context, carbon-based nanomaterials and graphene sheets are the most promising candidates for realizing supercapacitors because of their high electrical conductivity, surface area, and chemical inertness. Other materials can be combined with the carbon nanomaterials (such as nickel hydroxide, manganese dioxide, transition metals, solid-state electrolytes) to improve the inherent properties of carbon, along with three-dimensional porous topologies, asymmetric electrode design techniques, and series/parallel configurations to enhance the energy density of supercapacitors [13,118].

7.2. Wireless data communication

As we head towards near real-time sensing of physiological and biochemical signals, the amount of data generated, stored, transmitted, processed, and analyzed is expected to grow exponentially [13,14]. Fig. 8 shows the overall data flow architecture in a typical multi-sensors network connecting the user to healthcare professionals for real-time feedback on health and fitness. For example, the wearable sweat sensors can continuously test the sweat produced and determine the levels of electrolytes or metabolites. The data from the sweat sensors (i.e. physical, biochemical, environmental, and location) can be stored locally in microprocessors with built-in memory units for several hours of operation, and then be transmitted wirelessly to a local area network and remote servers. Using smart data analytics, relevant information can be extracted and passed on to healthcare professionals for the assessment of health parameters and plan of action. This scenario can grow complicated when multiple users request access to a common wireless network, especially when individual users may be wearing a range of sensor arrays.

Within the wearables industry, data communication protocols are categorized into two groups: Bluetooth low energy (BLE) and near-field communication (NFC) [18]. Some of the other wireless communication standards include ZigBee, Z-Wave, ultra-wideband (UWB), Thread, NB-IoT, MiWi, EnOcean, ANT+, Wi-Fi, WirelessHART, Weightless, and RFID.

BLE technology was designed by the Bluetooth Special Interest Group (Bluetooth SIG) to provide low power consumption and is implemented in a wide variety of applications including healthcare, fitness, and home entertainment. It operates in 2.4–2.4835 GHz ISM band with bitrates ranging from 125 kbits/s to 1 Mbits/s for BLE 4.0. It can communicate wirelessly up to a distance of 100 m. Small data packet communication is typically based on the Generic Attribute Profile (GATT) over a low energy link. However, the SIG group defines several profiles for specific application use cases. An example is the Blood Pressure Profile (BLP) which is used for communicating with blood pressure measurement devices [123]. A number of recent wearable sweat sensing platforms have incorporated Bluetooth technology for wireless transmission of analyzed data from the sensing devices. For instance, a microcontroller (ATmega328p) with Bluetooth module has been used to send data from multiple impedance and open-circuit-potential sensors to a

mobile phone interface [72]. A fully integrated sensing array has been interfaced with a microcontroller and Bluetooth module to measure sweat metabolites, electrolytes and skin temperature [87]. The microcontroller (ATmega328p) with Bluetooth-enabled mobile handset has been used to trigger the iontophoresis circuit using its digital-to-analog-port [65]. Flexible printed circuit boards (PCBs) have been developed with Texas Instrument CC2541 BLE System-on-Chip for wireless monitoring of sweat alcohol and sodium levels [39,43]. Bluetooth wireless electronics (nRF51822, Nordic Semiconductors) has been interfaced with operational amplifiers for continuous measurement of sweat composition during cycling and running [94].

NFC operates at 13.56 MHz on an ISO/IEC 18,000-3 air interface with bitrates ranging from 106 kbits/s to 424 kbits/s. Typically the wireless range is 10 cm or less. This technology is used to transfer short pieces of information to other NFC supported devices (e.g. smartphones). The NFC has two modes of operation: passive and active. In passive mode, the initiator (reading device) starts the communication and the target NFC device draws power from the initiator's electromagnetic field and provides the response data. In the active mode, however, both the initiator and target have their own power sources for data communication [124]. NFC devices are typically used in contactless payment, identity keycard, and tagging systems [125]. Wearable sweat sensors have also incorporated NFC electronics for wireless communication of analyzed data to handheld devices. For instance, NFC coil has been integrated with an epidermal microfluidic device for the capture, storage, and analysis of sweat electrolytes in aquatic settings [69]. NFC electronics with a magnetic loop antenna has been interfaced with a smartphone to take digital images of colorimetric assays for the measurement of sweat biomarkers (e.g. glucose, lactate, chloride, and hydronium ions) [126].

7.3. Signal processing and smart data analytics

Signal filtering and noise elimination is an important aspect of any electronic sensor design which attempts to extract the raw signal from background noise. In wearable devices, a major contributor to signal noise is motion, especially in devices fabricated from flexible materials where there can be issues with lead connections and impedance fluctuations [14,15]. In multiplexed sensing devices, noise can also appear as interference between various sensing methods. For instance, interfering electric fields from nearby electrical sensors could present itself as noise in one of the measurements [7,116]. High-frequency noise filtration occurs at either the software or the hardware front-end level by means of a low-pass filter.

The display and integration of the recorded data on user-friendly gadgets (such as PDA, smartphone, and smart watches) is important towards winning the consumer's loyalty. The end user may not prefer carrying a dedicated screen to read the sensors' data during the period of active device operation. Rather it is more convenient to transmit the recorded data on to displays of portable phones and watches, using dedicated apps that display the data in an understandable format. Most of the published articles demonstrate some form of communication with phones and watches to display the sensors' data [20,64,65,69]. The design of apps that can remotely initiate sensing and record data is prevalent today. As such, in sweat sensing it will be impactful to build apps that can interpret and map the sensor data into conclusive health or fitness parameters (such as hydration level, tiredness, etc.). This can be accomplished through rigorous field tests on a diverse population of wearers that generate look-up tables, calibration curves, and feedback control algorithms to translate the sensors' data into useful information.

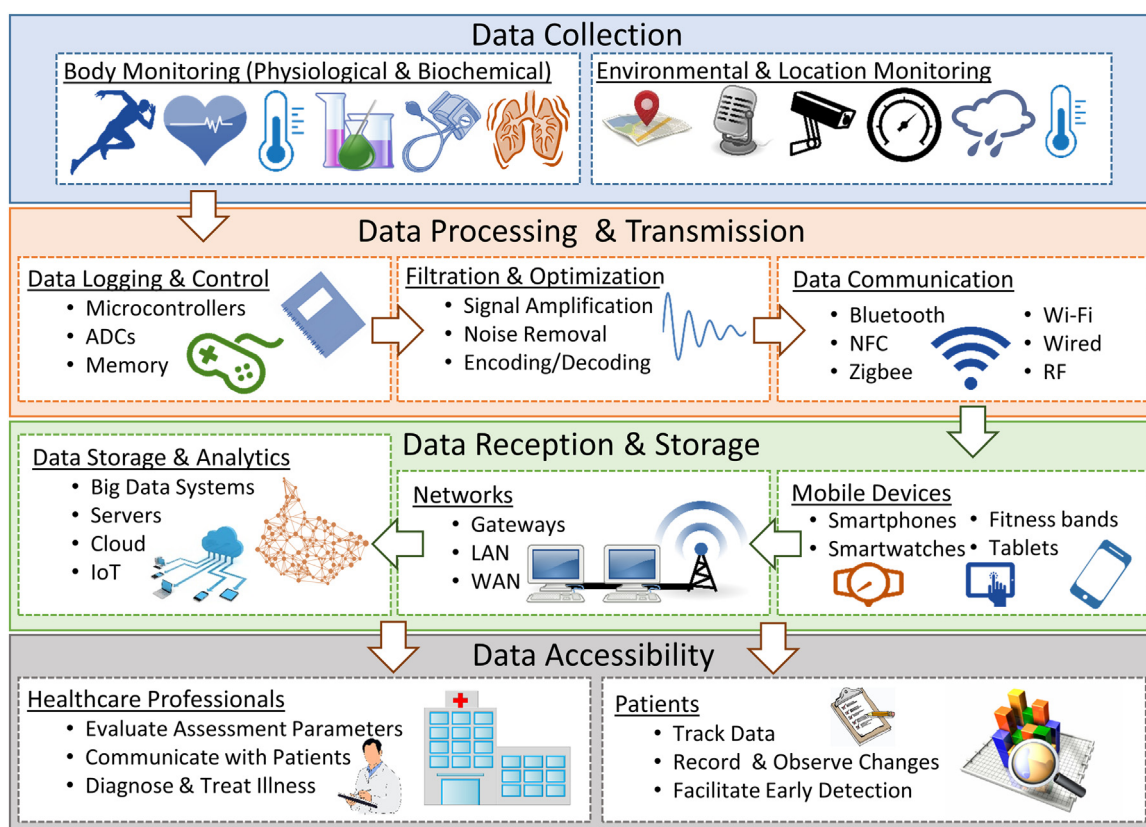


Fig. 8. Data flow architecture in a multi-sensor network. Various wearable sensors worn by the user gather the physiological, biochemical, environmental, and location signals. The data from all sensors is passed through analog and digital electronics and relayed wirelessly to the local area network and remote servers. Smart data analytics is used to extract relevant information and store in the cloud servers. The information is accessible to healthcare professionals who can evaluate the different assessment parameters and inform the user about any remediation steps.

As high-density sensor arrays are emerging for the ubiquitous monitoring of physiological parameters, there is a large amount of low-quality data produced from sensors. Wearable sweat sensing could generate the “big data” comparable to those in the fields of genomics, banking, personal finance, e-commerce, or social networks. Tools in big data analytics (e.g. Hadoop), data mining, deep learning, and artificial intelligence are available to extract relevant analytical information and generate timely alerts for the wearer or caregiver in case of unexpected data trends. Output-driven feedback control systems have been employed to alter the sensing parameters based on the existing datasets [78]. The ability to continuously monitor and relay information to healthcare professionals for feedback and advice has relevance in clinical settings where data is needed immediately (emergency rooms), passively (in-patient settings), or remotely (out-patient settings) (Fig. 8).

8. Commercialization efforts in wearable sweat sensing

As listed in Table 4, a number of companies have vested interests and intellectual property in the area of wearable sweat sensing. A brief description of the companies follows here.

Eccline Systems was founded in 2013 by Prof. Jason Heikenfeld and the University of Cincinnati to commercialize their technologies on advanced sweat sensing. Eccline's sweat sensor platform could identify how patients respond to certain drugs, and thus help to optimize pharmacotherapy at an individual level. Eccline Systems has over 100 patents (issued and filed) on the topics of continuous, on-body sweat measurement with a recent collaboration with chipmaker Maxim Integrated Products.

Nix Biosensors came out of the Harvard Innovation Launch Lab and has built a sweat-based electrochemical patch sensor to monitor the hydration levels and electrolyte loss of individuals. Their sensing platform is geared towards athletes, soldiers, and laborers who require optimal hydration for safety and performance. The Nix hydration biosensors are designed to be light-weight and stand-alone with real-time testing and single-use applications.

CFD Research Corporation is applying its proprietary technology of sugar-powdered Bio-Battery™ to wearable sweat sensors that monitor the lactate levels in sweat. It is collaborating with the U.S. Air Force towards real-time monitoring of dehydration and muscle fatigue in soldiers.

Kenzen is developing patch technologies to perform real-time sweat analysis of at-risk individuals towards reducing stress and injuries. Their disposable patch can be worn on the torso or upper arm to monitor the heart rate, body temperature, sweat rate, and activity. A monitoring station and mobile app stores and analyzes the data to give real-time feedback on performance or vitals.

Biolinq, formerly called *Electrozyme*, has developed a wearable, on-the-skin tattoo that serves as an electrochemical sensor platform for sweat sensing applications. Their temporary tattoo is designed to measure the metabolic substances in sweat and provide clues about hydration levels, electrolyte balance, and fatigue.

Graphwear Technologies has developed a sweat assessment patch to track the glucose and electrolyte levels of athletes in professional football teams. The hydration patch alerts the wearer when to replenish their fluids. NFL players have participated in their pilot studies. There is interest to develop the technology into a Class 2 medical device for glucose monitoring of diabetic patients.

Table 4

List of companies with commercial interests in the area of wearable sweat sensing.

Company	Location	Website	Commercial Intent
Eccrine Systems, Inc.	Cincinnati, OH	www.eccrinesystems.com	Health, Safety
NIX	Boston, MA	www.nixbiosensors.com	Hydration
CFD Research Corporation	Huntsville, AL	www.cfdr.com	Health Monitoring
Kenzen	San Francisco, CA	www.kenzen.com	Worker Safety
Biolinq	San Diego, CA	www.biolinq.me	Glucose Monitoring
Graphwear Technologies	San Francisco, CA	www.graphwear.co	Health Monitoring
TE Connectivity	Tredyffrin, PA	www.te.com	Fitness Tracking
La Roche-Posay Laboratoire Pharmaceutique	La Roche-Posay, France	www.laroche-posay.us	Health
PharmChek	Fort Worth, TX	www.pharmchek.com	Drug Testing
Alcopro	Knoxville, TN	www.alcopro.com	Drug Testing
Epicore Biosystems	Cambridge, MA	www.epicorebiosystems.com	Fitness Tracking
Droog/Nissan	Amsterdam, The Netherlands	www.droog.com	Hydration
BACtrack	San Francisco, CA	www.bactrack.com	Alcohol Monitoring
Nemaura Medical	Loughborough, United Kingdom	www.nemauramedical.com	Glucose Monitoring
Scram Systems	Littleton, CO	www.scramsystems.com	Alcohol Monitoring

TE Connectivity is one of the largest manufacturers of sensors for a wide variety of applications (e.g. pressure, temperature, humidity, force, vibration). It has developed a piezo film sleep sensor that monitors multiple functions such as sleep cycles, respiration rate, heart rate, and physical activity. Sweat monitoring sensors could be integrated in several of their existing piezo film sensors.

La Roche-Posay has released a wearable sensor that can measure and track the pH of skin. Healthy skin has a 5.5 pH and deviations from this ideal pH level could lead to inflammation and skin conditions such as eczema and acne. Their flexible device collects a small sample of sweat from skin pores and reveals the skin pH within 15 min. A Skin Track™ pH app is available to read the pH measurements and rate the skin health with appropriate recommendations.

Pharmchek has developed a proprietary absorbent pad to collect perspiration that then can be sent for laboratory analysis. A polyurethane film allows the small molecules to pass through while capturing the large molecules in the absorbent pad. The sweat analysis panel is designed to detect drugs of abuse such as cocaine, opiates, methamphetamine, marijuana, oxymorphone, and hydromorphone.

Alcopro has developed a sweat patch drug test system that is available for specific programs in law enforcement, drug diversion programs, treatment programs, re-entry programs, and court programs. The system consists of a sweat collection pad that is worn for seven days and eventually tested off-site in a certified laboratory. Five common drugs of abuse can be detected by their system: marijuana or THC, cocaine, opiates, amphetamines/methamphetamines and PCP.

Epicore Biosystems has built skin-like, microfluidic sweat sensing platforms that can directly analyze droplets of sweat. The company was founded in 2017 by the team of Prof. John Rogers from Northwestern University. Epicore Biosystems has several industry and federal government partners to push wearable microfluidics in the management of hydration and skincare.

Nissan worked with a design company, *Droog*, to develop a sweat-sensing textile for car seats and steering wheels in Nissan Juke vehicles. The textile fabric 'soaks up' the sweat from the driver's clothing and changes color when in contact with perspiration – turning blue when the driver is hydrated and yellow when the driver is dehydrated. This allows the vehicle to sense if the driver is dehydrated (a condition that can compromise physical and mental abilities) and alert them in a timely manner to avoid any risky situations.

BACtrack has a series of breathalyzers for accurate and reliable determination of alcohol in the blood. The company recently launched a wrist-based wearable alcohol tracker to measure the alcohol content in the sweat and send notifications when a certain limit is reached. This wrist-based tracker is designed to work as

a stand-alone or integrated with the Apple Watch and avoids the inconvenience of blowing air into breathalyzers.

Nemaura Medical has developed SugarBEAT™ which is a proprietary skin patch technology for continuous glucose monitoring of diabetic and pre-diabetic patients. Their platform provides a mobile, non-invasive, needle-free approach to glucose measurements by using glucose molecules from interstitial fluids. After an initial 30-minute warm up, their patch gives the glucose readings every five minutes for the entire day. The SugarBEAT™ market launch was in the United Kingdom (2019) with a daily price comparable to glucose meters and test strips.

Scram Systems has a range of products related to alcohol monitoring including CAM™ bracelet to report alcohol consumption through transdermal testing. Their systems are supported with training programs and data analytics for community correction agencies and alcohol-involved offenders. The electronic monitoring is accompanied by mobile apps and program management center to manage the recorded data, allow automated reminders, check-ins etc. for better user engagement.

9. Exemplary wearable sweat sensors

In recent years, the design and implantation of wearable platforms has undergone noticeable advancements in almost all domains of research and development. This has improved the following features: (i) multi-functionality to detect several parameters of interest at near real-time, (ii) on-body compliance to design comfortable and on-skin devices with appropriate flexibility and robustness, and (iii) system integration to fabricate all the electrodes, sensors, signal processing circuits, and wireless communication modules on a single, non-rigid platform. Fig. 9 shows some examples of sweat sensing platforms for various applications, such as the detection of sweat caffeine levels (Fig. 9a), sweat glucose levels and physiological parameters (Fig. 9b), sweat ethanol levels (Fig. 9c), and sweat rate/composition (Fig. 9d). Table 5 highlights the technical aspects of these sweat sensors. Below we summarize some of these efforts with exemplary applications of wearable sweat sensors.

An epidermal tattoo technology was developed to detect the levels of sodium in sweat [43]. On a tattoo paper, an insulator coating is initially screen printed. Next two-dimensional 'Tiger Face' was laser printed on the insulator-coated tattoo paper. This was followed by steps of screen printing the electrodes and contact pads. A sodium selective membrane cocktail was drop-cast on the carbon electrodes which served as the primary sodium sensor. The Na-tattoo sensors, connected with wireless transceivers, were tested on 10 healthy humans who were subjected to 30 min of cycling, 3 min of cool-down, and 3 min of complete rest. It was shown

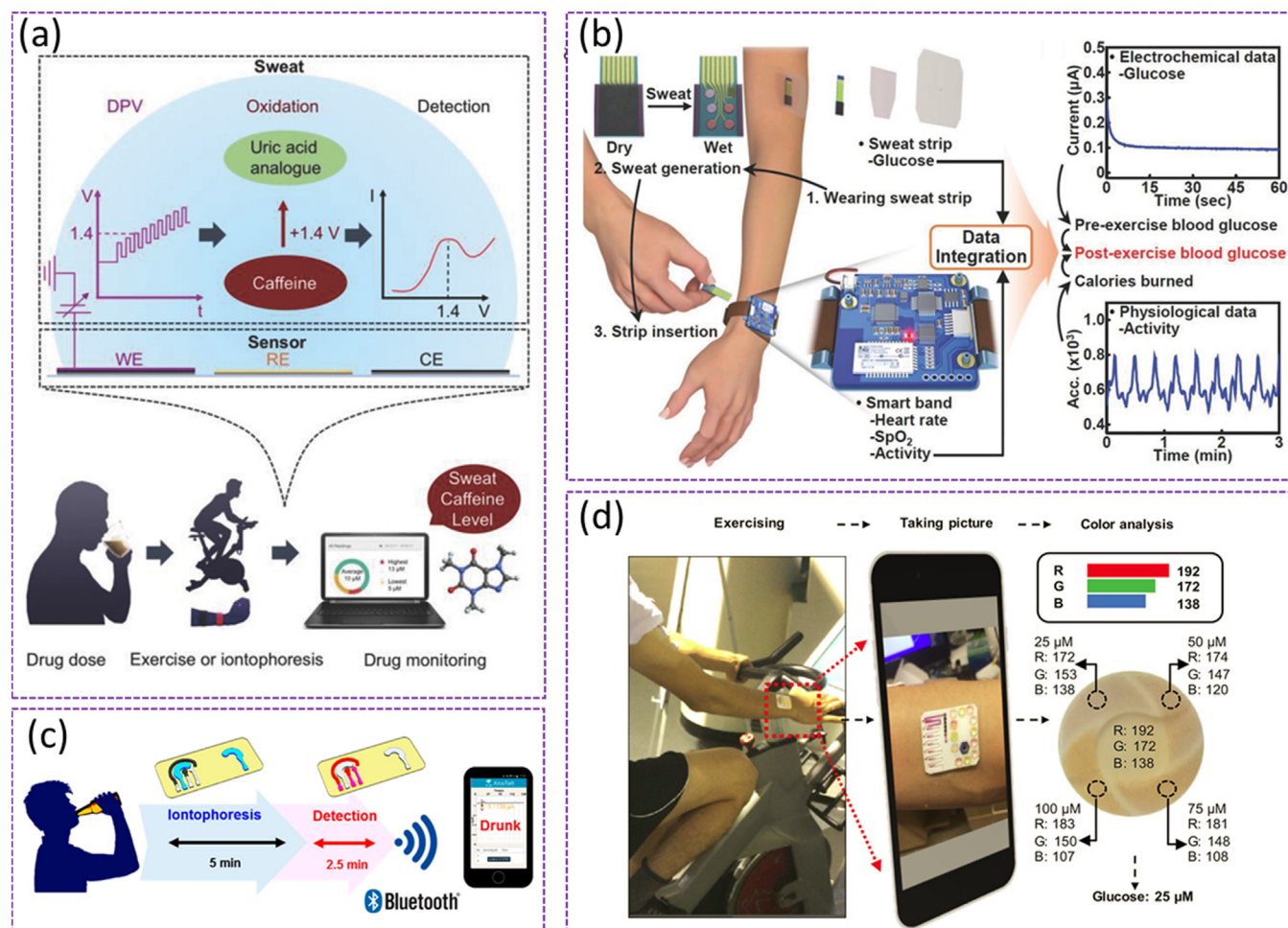


Fig. 9. Examples of sweat sensing applications. (a) A wearable sweatband detects the sweat caffeine levels after the consumption of caffeine, induction of sweat secretion, and differential pulse voltammetry. The potential between the working electrode (WE) and reference electrode (RE) is linearly swept with regular pulses. The oxidation of caffeine produces an oxidation peak around 1.4 V that is read out by the printed circuit board and transmitted wirelessly. Reprinted (adapted) with permission from ref. [46]. Copyright (2018) John Wiley and Sons. (b) An integrated system combines glucose sensing strips with a wearable smart band to monitor heart rate, blood oxygen saturation level, and activity. Sweat is generated and collected in the glucose strip. The electronics in the smart band records electrochemical and physiological data both pre-exercise and post-exercise. Sweat glucose levels correlate well with blood glucose levels as tested on multiple human subjects. Reprinted (adapted) with permission from ref. [5]. Copyright (2018) John Wiley and Sons. (c) A tattoo-based alcohol sensor integrates iontophoresis and amperometric detection of ethanol to provide a real-time readout of alcohol consumption via a Bluetooth module. Reprinted (adapted) with permission from ref. [39]. Copyright (2016) American Chemical Society. (d) A soft, on-skin microfluidic system integrates sweat collection and colorimetric chemical analysis. The system measures the loss of sweat, sweat rate, pH, temperature, and concentrations of glucose, chloride, and lactate. Devices are worn on the forehead, torso or forearm during exercise to produce distinct color changes (with unique RGB values) in the presence of sweat biomarkers that are subsequently captured by a smartphone and quantified into relevant information. Reprinted (adapted) with permission from ref. [82]. Copyright (2019) American Chemical Society.

that the sodium sweat sensors had a rapid and reversible response to varying sodium concentrations (0.1–100 mM), while reaching a steady state within 10 s. The sodium sweat sensors displayed good mechanical resilience as they maintained their sensing properties while subjected to various mechanical deformations and bending strains. The wireless transceiver (microcontroller and Bluetooth module) transmitted the data about sodium dynamics over 10 m and removed the need for wires or connectors that may interfere with the human activity.

A soft, epidermal microfluidic device was developed to directly harvest the sweat from the skin's surface and perform colorimetric tests for four analytes in sweat: pH, lactate, glucose, and chloride [19]. Sweat was accessed using a medical-grade acrylic adhesive layer with micro-machined openings, which then passed through PDMS microchannels and collected into reservoirs. A range of compliance tests ensured that the adhesive layer attached to the skin with minimal irritation and appropriate compatibility. The flow of sweat in the device was revealed by using cobalt chloride (applied as a coating within microchannels) as a colorimetric indicator. The

enzymatic reactions were used to detect the concentrations of glucose and lactate using glucose oxidase and lactate dehydrogenase/diaphorase, respectively. The pH was monitored by universal colorimetric dyes such as methyl red, bromothymol blue, and phenolphthalein. Chloride detection was based on the competitive binding of Fe²⁺ and Hg²⁺ with 2,4,6-Tri(2-pyridyl)-s-triazine (TPTZ) which produced a color change from transparent to blue in the presence of chloride ions. An on-chip magnetic loop antenna with NFC electronics allowed communication with external devices. A smartphone was used to capture the images from the colorimetric assay and convert them to quantitative values. Tests were conducted on human subjects with devices placed on their lower back and forearm. The sweat rate, sweat volume, and concentrations of the four analytes measured from the device were in agreement with laboratory tests using absorbent pads.

An integrated sensing array with a flexible printed circuit board was developed to simultaneously detect levels of sodium, potassium, glucose, and lactate in sweat [97]. Flexibility of the electronics and proper skin contact was ensured by using a polyethylene

Table 5
Summary of the exemplary wearable sweat sensors.

Analyte	Transducer	Device	Communication	Laboratory testing	Human testing
Sodium [43]	Ion selective membrane	Epidermal tattoo on rigid plastic substrate	Bluetooth v2.1 + EDR (2.4 GHz)	Electrochemical analyzer, artificial sweat	Cycling bout (30 min), Ramp resistance
pH, lactate, glucose, chloride [19]	Colorimetric indicators in hydrogel matrix	Skin-worn epidermal microfluidic device	NFC electronics, magnetic loop antenna	Absorbent pads, finite element analysis	Intermediate activity, cycle ergometer (1 hour)
Sodium, potassium, glucose, lactate [97]	Ion selective membranes, PEDOT:PSS	Smart wristband and headband	ATmega328 P, Bluetooth transceiver	Gauze, artificial sweat	Constant load exercise, graded-load exercise, cycle ergometer (20 min)
Alcohol [39]	Alcohol oxidase enzyme	Skin-worn epidermal tattoo	TI CC2541 Bluetooth LE	Chronoamperometry, cyclic voltammetry, phosphate buffer	Iontophoresis (5 min), Resting (5 min)
Sodium, chloride [65]	Ion selective membrane, Ag/AgCl electrodes, PEDOT:PSS	Smart wristband on a rayon pad	ATmega328 P, Bluetooth transceiver	Iontophoretic drugs, sweat-rate sensor	Healthy and cystic fibrosis patients (20–25 min)
Glucose, heart rate, SpO ₂ , activity [5]	Carbon and Ag/AgCl electrodes, glucose oxidase (GOx)	Sweat analysis strip, wearable smart band	Atmega328 P, Arduino UNO, pulse oximeter	Chronoamperometry, electrochemical analyzer, artificial sweat, glucometer	Pre- and post-exercise on cycle ergometer, foot bath, skipping rope, burpee test
pH, skin temperature [2]	graphite-polyurethane composite, Ag/AgCl electrode	Stretchable, wireless pH sensing system	NFC (13.56 MHz), stretchable RFID antenna, RFID transponder chip	artificial sweat, DMEM solution, cyclic voltammetry, EIS, potentiometry, vector network analyzer	Smartphone app (SenseAble) to display pH data and temperature
Stress, cortisol [20]	organic electrochemical transistor, PEDOT:PSS	Electrochemical transistor with cortisol-sensitive polymeric membrane	Drain current measurements using electrical contacts to the wearable device	artificial sweat, current meter, cyclic voltammetry, Human Cortisol ELISA kit	intensive outdoor running exercise (20 min), on-body sprayed samples
Hydration metrics, chloride, skin temperature [69]	Microfluidics, colorimetric food dye, silver chlorinate	Epifluidic underwater sweat collection and thermography platform	NFC chip, magnetic loop antenna, indicator LED, temperature sensor	FEA, Tensile strength, skin adhesion tests, absorbent pads, chloridometer	IRONMAN Triathlon, swimming (45 min), biking (30 min)

terephthalate (PET) substrate. Amperometric sensing of glucose and lactate was accomplished by incorporating glucose oxidase and lactate oxidase within a permeable film of chitosan. Sodium and potassium were measured by potentiometric sensors using ion-selective membranes. The output signals from sensors were passed through transimpedance amplifiers and low-pass filters. A microcontroller and Bluetooth module with a mobile application for data display was included. Human subjects were asked to perform constant-load or graded-load exercise and the levels of the four analytes were measured at real-time. With the start of perspiration, there was a visible increase in the skin temperature, sweating rate, and sodium levels in the sweat. The concentration of sweat sodium served as an important biomarker for dehydration. However, the patterns of lactate, glucose, and potassium excretion varied among subjects and needed further studies to identify noticeable trends with vital signs.

A temporary tattoo with flexible electronics was developed to measure alcohol levels in sweat [39]. Even though consumed alcohol can be detected from most of the bodily fluids, the determination of alcohol levels from human breath or sweat by non-invasive and on-the-spot technique is most desired. In these cases, the Blood Alcohol Concentration (BAC) is indirectly estimated by the breathalyzer or wearable sweat sensors. A wearable temporary-tattoo paper was incorporated with screen printed electrodes, along with a flexible printed electronic circuitry to transmit the data wirelessly to a remote workstation (Fig. 9c) [39]. Sweat was induced by delivering pilocarpine below the skin by the iontophoresis method. The sweat ethanol level was measured by amperometric sensing using an alcohol-oxidase enzymatic electrode and a Prussian Blue electrode transducer. There were five electrodes on the sensor chip: two iontophoretic electrodes for inducing sweat and three amperometric sensing electrodes for ethanol detection. The sensor was highly selective towards ethanol

even in the presence of other analytes such as glucose, uric acid, creatinine, and lactate. The experiments showed that the measured sweat ethanol levels correlated relatively well with the blood alcohol concentration estimated from the breathalyzer. It was noticed that the output of the breathalyzer was dependent on the body weight and alcohol metabolism rate of individuals. Similarly, the output of this sweat sensor was dependent on the skin permeability, sweat flow rate, and sweat compositions of different people. These variations could be calibrated by using a large pool of human subjects tested under varied conditions. The entire alcohol-tattoo system has sufficiently small form factor to be incorporated in places (such as cars, bars) to help people measure their alcohol levels with adequate privacy and deter unsafe driving on the streets.

An autonomous platform was reported that can induce sweat secretion and detect the levels of three analytes (i.e. glucose, sodium, and chloride ions) in the sweat sample [65]. The sodium and chloride levels are diagnostic markers for cystic fibrosis while sweat glucose levels, if correlated with blood glucose levels, can potentially be used for diabetic screening. Here the substrate was polyethylene terephthalate (PET) which is mechanically flexible and suitable to form a stable contact between the skin and sensor pads. Two sets of electrodes were patterned on the same substrate: iontophoresis electrodes to stimulate the sweat glands and sensor electrodes to analyze the three analytes on-site. The iontophoresis electrodes used a thin layer of hydrogel (containing an agonist agent) with stainless steel contacts to electrically interface with the skin. The sensor electrodes used a thin rayon pad to interface with the skin. For sweat analysis, potentiometric sodium and chloride sensors with ion-selective films were used, along with an amperometric glucose sensor that uses glucose oxidase. A wireless flexible printed circuit board was built to fully integrate the iontophoresis and control circuits, analog frontends, low-pass filters, microcontroller, and Bluetooth transceiver. The system was tested on six

healthy volunteers (Na^+ : 26.7 μM and Cl^- : 21.2 μM) and three patients with cystic fibrosis (Na^+ : 82.3 μM and Cl^- : 95.7 μM). The results confirmed that the sweat chloride levels in cystic fibrosis patients ($> 60 \mu\text{M}$) is higher than in healthy individuals ($< 30 \mu\text{M}$). In addition, the sweat chloride levels were higher than the sodium levels in cystic fibrosis patients, in contrast to healthy individuals who have higher sweat sodium levels compared to sweat chloride levels. This fact helped justify the value of the system as a diagnostic assay for cystic fibrosis where it is possible to conduct real-time and simultaneous screening of sodium and chloride levels in sweat samples. Preliminary tests on healthy subjects (before and after glucose consumption) showed good glucose levels' correlation in the sweat and blood.

A wearable health monitoring system was reported that consisted of disposable strips for sweat glucose analysis and a smart band to monitor the vital signs (heart rate, blood oxygen saturation level (SpO_2)) and physical activity (Fig. 9b) [5]. The disposable strip had microfluidic channels to accumulate the sweat by capillary forces, separation film embedded with a glucose sensing strip, and a hydrochromic layer (film of sputtered magnesium) that becomes transparent in the presence of sweat. The glucose sensing strip had an integrated temperature sensor, three working electrodes (WE) made of carbon, and two reference electrodes (RE) made of Ag/AgCl. The output of glucose sensors was passed through a transimpedance amplifier and digitized by the analog-to-digital converter of a microcontroller. Physical activity was monitored by three-axis accelerometers. Photoplethysmogram (PPG) was conducted by a pulse oximeter to detect changes in blood perfusion within the dermis and subcutaneous skin tissues. Sweat was generated by dynamic methods (i.e. skipping ropes, cycling, or burpee test) or static method with no exercise (i.e. foot bath). Sweat was collected from the forehead, arm and back of healthy human subjects for five days. During pre-exercise and post-exercise, the vital signs (heart rate and SpO_2) and blood glucose levels were monitored with varying intensities of workout. The blood glucose levels, measured by Accu-Chek Performa glucometer (Roche, Switzerland), correlated well with sweat glucose levels (correlation factors within range of 0.01–0.02) for each subject both during pre- and post-exercise. The wearable smart band system accurately measured the post-exercise blood glucose levels which was important for predicting hypoglycemic risks during intense workouts.

A stretchable biosensor with flexible antenna was developed for monitoring the pH levels in sweat [2]. It is challenging to design a completely flexible wearable system where all sensing and communication devices are non-rigid and integrated on-chip. The stretchable pH sensor used graphite-polyurethane (1:1 ratio) as the pH sensitive electrode and Ag/AgCl paste as the reference electrode [2]. A stretchable radio-frequency identification (RFID) antenna was fabricated for Near Field Communication (NFC) that has an inductance of 1.88 μH and resonant frequency of 13.56 MHz. The antenna is directly cut from a flexible polyimide film having a copper clad. A RFID transponder chip was used as interface between the pH sensor and antenna. Mechanical resiliency was measured by stretching the system from two sides using stepper motors and simultaneously monitoring the sensor electrode resistance and S-parameters of the antenna. The wireless pH sensor displayed a range of 5–9 pH, sensitivity of 11.13 mV/pH, response time of fewer than 8 s, and communication distance of 2–3 cm. The data on pH and skin temperature was displayed on a custom smartphone app called "SenseAble".

An organic electrochemical transistor (OECT) was reported to measure the cortisol levels in sweat [20]. Cortisol and adrenaline in bodily fluids are known biomarkers for stress. Thus the continuous monitoring of cortisol can help us maintain the overall homeostasis of the human body and help cope with high-stress situations that can cause detrimental effects to the human body. Here the

OECT had a semiconducting polymer channel (made of PEDOT: PSS) and Ag/AgCl gate functionalized with a cortisol-selective membrane. In an OECT, the electrolytic ions surrounding the gate region can dope or de-dope the volume of the semiconducting polymer channel and alter its conductivity. In the absence of cortisol, the ion-permeable membrane produced a large change in the drain current while the presence of cortisol blocks the membrane and reduces the change in drain current. The cortisol sensing patch was prepared by stacking all the layers (i.e. OECT, molecularly-selective membrane, microcapillary channel arrays, sample reservoir, and hydrophobic protection layer) on a flexible elastomer substrate. The fabricated patch was placed on a volunteer's forearm to measure the cortisol levels after 20 min of outdoor running. Changes in the drain current of OECTs were measured as a function of time directly on the skin which were interpolated to provide the cortisol levels in sweat.

A soft, epidermal-microfluidic device was developed to measure the hydration metrics of aquatic athletes with sweat collection and skin thermography being performed under the water [69]. The sweat loss in swimmers is traditionally estimated by measuring the changes in body weight. The traditional method is erroneous because of unavoidable fluid loss by other channels such as urination, evaporation, and water ingestion. Here the epifluidic device was made on a skin-compatible poly(styrene-isoprene-styrene) (SIS) elastomer substrate and consisted of microfluidic channels for sweat collection with minimal contamination and adhesive materials for waterproof bonding to the skin. The underwater sweat collection was enabled by the unique barrier properties of the SIS, such as its hydrophobicity, low air permeability, small dimensions of the microfluidic channels, and differential hydrostatic pressure. The robustness of the device's adhesion was rigorously tested by mechanical deformation experiments and finite element analysis (FEM) of the stress and strain distributions. The near field communication (NFC) electronics consisted of a copper-based magnetic loop antenna, NFC chip, blue light emitting diode, resistors, capacitors, and on-board temperature sensor. The device was tested during practice sessions at the IRONMAN Triathlon World Championship by placing them on the ventral forearm of the subjects before, during, and after swimming. The devices were imaged after 45 min of swimming (2.5 km) or 30 min of biking (14 km). The skin temperature was measured by the temperature sensor, infrared camera, and thermocouple reader. Sweat chloride concentrations were detected by color changes in the channels pre-filled with a silver chloranilate reagent. The sweat volume per area inferred from the colorimetric assay showed good correlation with calculations based on the mass gain from absorbent foams and body weight loss.

10. Future challenges and outlook

The abovementioned examples of sweat sensing applications show a clear trend towards continuous, real-time sweat analysis using skin-conformable, flexible devices with integrated fluidics and electronics. While rapid progress has been made in the materials and device area with a myriad of technologies, there are realistic challenges still associated with wearable sweat sensors.

One challenge lies in the continuous collection of sweat and monitoring of its composition. The slow excretion rate of sweat limit the sample volume, and the problem is compounded by uncontrolled evaporation, respiration, and transcutaneous water reabsorption. Sample contamination can pose challenges for measurement accuracy, especially in outdoor settings where there is unavoidable exposure to various fluids and toxins. Without fast sampling, intermixing of old and new sweat within the sensing device is an issue for real-time monitoring of the fluctuations in analyte concentrations. Modelling the rate at which the body excretes sweat is still challenging as there is significant variability

across different locations of the human body and across different individuals. To address the above issues, a wearable sweat sensing patch was developed to simultaneously measure the sweat rate and dynamic changes in sweat constituents (Na^+ , K^+ , pH and Cl^-) [72]. In their study, microfluidic channels, bonded to a PET substrate, were used to continuously guide the produced sweat into 14 μL reservoirs by capillary action. Ion sensing electrodes, integrated within the microfluidic device, measured the electrical impedance which was then correlated to the sweat rate in the arm region (at 0.4–2 $\mu\text{L}/\text{min}$ for a collection area of 5 mm diameter). During a biking exercise (constant biking power of 150 W), the dynamic fluctuations in Na^+ and Cl^- concentration followed the general trend in sweat rate. Another group developed an electronic wearable sensor patch to continuously measure the sweat composition (i.e. Na^+ , lactate, and pH) [94]. In their study, microfluidics was employed to channel the sweat onto absorbing paper pads. Flexible electrochemical sensors measured the analyte concentrations at near real-time. During the biking exercise, mean values of Na^+ , lactate, and pH increased with time, and gradually decreased during the recovery period. For these and other wearable sweat sensors, it is important to expand the tests to population levels (from different age groups, genders, race, ethnicity, and geographical locations) where some sort of normalization and optimization of sweat production can be performed. Furthermore, the nature of physical exercise could be expanded (e.g. having varied resistance levels and longer durations) and complemented with non-physical methods of sweat generation (e.g. stress induction, changes in humidity or temperature). As more field-ready data becomes available, better predictive models can be built for the reliable mapping of spatial and temporal changes in sweat production, sampling, collection, and analysis [7,11,13,18,49].

Most prototypes of wearable sweat sensors are tested in the laboratory using artificial sweat and a challenge lies in validating these results in the field. Such artificial eccrine perspiration products are commercially available (e.g. Pickering Laboratories, Mountain View, CA, USA). These formulations typically contain metabolites (lactic acid, uric acid, urea, ammonia), minerals (sodium, potassium, chloride, calcium, magnesium, zinc, iron, copper, nitrate, sulfate), and various amino acids. Besides conducting device characterization with artificial sweat, the wearable sweat sensors should be tested on-body for prolonged time periods (several hours to days) during a broad range of physical, chemical, environmental and health conditions [41,69]. Proper estimation of sensor performance should be performed with regards to its on-body resiliency to mechanical stress, response time in data collection, stability or drift under changing environmental conditions, and calibration procedure especially during long-term, repeated use of sensors [18].

Another challenge lies in adequately evaluating the biocompatibility of wearable sweat sensors. Tests should be conducted to ensure the materials used in the devices (e.g. pilocarpine in Fig. 6a) do not produce any toxic effects on the individual within the time of wearing the device [15,54,69]. The biocompatibility matrix indicates that surface devices that are in contact with the skin should be tested for cytotoxicity, sensitization, and irritation or intracutaneous reactivity [15,127]. The cytotoxicity of the sensor materials is generally tested on cell cultures by direct contact, agar diffusion, colony formation or cell viability tests. Sensitization is checked to ensure the sensor materials do not induce allergic reactions where the typical tests are the Guinea Pig Maximization Test, Closed Patch Test, and the Murine Local Lymph Node Assay. The Primary Skin Irritation Test and the Mucous Membrane Irritation Tests are performed to test the skin irritation (edema and erythema) from topical use of the device material for a prolonged time period.

Wearable sweat sensing platforms are inherently power-hungry and a challenge remains on finding the best method to power these

devices for long time periods [13]. In the near future, there is no clear winner to replace conventional lithium-ion batteries. Besides the hunt for new energy generation alternatives that are compatible with wearable sweat sensors, some power-saving solutions could be investigated to smartly use and prolong battery life. These solutions include the use of intelligent power allocation algorithms, low-power and energy-efficient modules, and renewable energy resources on-chip [6]. Besides challenges in power generation and management, the options for wireless data communication are limited. Both BLE and NFC communication technologies are satisfactory as proof-of-concept demonstrations for wearable sweat sensors, but may not be appealing for futuristic sweat sensing systems, which are envisioned to be highly dense, operationally complex, and power-hungry. BLE enabled devices are not power efficient and require to be within 100 m of the central station. NFC enabled devices need to be in close proximity to the central station and user intervention is often required to collect data from the NFC devices. To overcome the deficiencies of BLE and NFC technologies, they may be combined with other wireless communication standards such as ANT+, RFID, and ZigBee. Smarter and adaptive use of these communication technologies (BLE and NFC) can also improve their power efficiency. The sampling frequency can be reduced or the devices can be switched off when the wearable device is dormant; on the other hand, the sampling frequency can be increased for sensors for short durations when critical data is being recorded [6,13]. For instance, sweat sensors can be activated or 'awakened' to collect data only during periods of critical human activity (such as running, walking or sleeping) [70]. Instead of transmitting all the gathered data from sweat sensors, it may be efficient to relay only the relevant or crucial information to the wearer. It may also be useful to deploy deep learning or artificial intelligence modules to understand when and how to effectively collect data from the various electrochemical or electrical sweat sensors. In addition, by employing cloud computing for storing and processing sensors' data, it is possible to relax the on-chip memory requirements in BLE or NFC enabled devices.

Another set of challenges towards the commercial adoption of wearable sweat sensors lies in understanding product aesthetics, pricing models, and consumerism. The consumer electronics market, particularly of smartphones and smart watches, have shown the value of aesthetics in enhancing the likeability of a product. Today the companies in the sweat sensing arena have put forth their products with enviable aesthetics and companion apps (Table 4). As an example, the concept of transparent electronics has been introduced to provide a rationale for visibly clear, self-destructive sensors. These optically transparent electronics can be made on substrates such as carbon-based materials, metal oxides, or conducting polymers. In general, future wearable (physical and chemical) devices need to be aesthetically pleasing for mass adoption, light-weight but with multi-functional attributes, and inconspicuous when worn by the user. The acceptance and adoption of a wearable sweat sensing product depends on these factors of aesthetics and physical attributes beyond the actual analytical performance. Consumers today already have a number of vendor options and the pricing will predictably grow competitive in the near future. In the sweat sensing market, we expect the advent of pricing charts for wearable devices based on the exact electrolytes and metabolites to be detected similar to those available during blood analysis. The pricing charts may include options to select wearable devices based on number of functions, number of uses, size or weight, accuracy, selectivity, and sensitivity. Further studies are needed to understand the different tradeoffs in the sociology of technology adoption and cost-versus-value proposition for the consumer. Privacy and protection of the wearer's data will be important aspects in coming times as wearables prove their value to consumers. The debate on the actual ownership of data gathered

from wearable sensors is in its infancy and we may see new regulations and data privacy acts similar to the ones formulated for social media companies.

It has been challenging for wearable sweat sensors to gain clinical validation with market acceptance. One impediment lies in the lack of sufficient data to establish correlation between sweat and blood biomarkers. The levels of sweat biomarkers obtained through any sensing modality should be rigorously compared with blood samples using gold standard techniques [5]. This would be useful, for example, in predicting imbalances in glucose levels during intense exercise towards preventing hypoglycemic shock [5]. Integrated sweat sensor arrays attached to various locations of the skin could enable the spatial and temporal mapping of pH and common ionic concentrations (sodium, potassium, chloride, calcium, ammonium) as a function of the physical activity or health condition requires [18,60,82]. Combining sweat analytics with physiological monitoring of relevant body parameters (e.g. physical activity, heart rate, body temperature, blood pressure, electrocardiogram (ECG), oxygen saturation, and respiration rate) will be the next milestone in wearable sweat sensing. In this context, a sweat analysis strip with smart wristband was recently developed to detect sweat glucose levels pre- and post-workout with simultaneous measurements of physical activity and vital signs (i.e. heart rate and blood oxygen saturation levels). A number of static and dynamic exercise routines were assigned a metabolic equivalent of task (MET) for further comparisons within the signal processing algorithms. There was correlation between the blood glucose levels, calories burnt, and sweat glucose levels both pre- and post-exercise, even though the sweat generate rate among subjects was dependent on the nature and duration of exercise [5]. Besides glucose, the measurement of other sweat analytes (e.g. pH, sodium, lactate, and cortisol) have been correlated with those in saliva during exercise. While lactate and sodium levels increased post-exercise, there were variations in the salivary cortisol levels, suggesting that cortisol may be more subject-sensitive [94]. The above studies point out an inherent challenge in correlating the dynamics of sweat sensing with those of other bodily fluids or physiological monitoring which lies in the observed variations across test subjects and nature/duration of exercise. Incorporating the sweat sensors with commercial platforms that monitor physiological parameters (e.g. chest straps, ECG shirts, adhesive patches, and blood pressure cuffs) could be one way towards seamless integration of data from all sensors. Smarter algorithms would be needed to choose the appropriate sensing window and best fit curves for making informed decisions on where, how, and what sensors to use for specific applications.

As the fields of wearable technology and Internet-of-Things (IoT) merge, the potential to overcome the limitations of *reactive healthcare* seems feasible by employing devices to monitor biochemical and physiological signals [13]. Towards this goal, the abovementioned examples of sweat sensing applications provide evidence of sensing systems which can be used for *proactive healthcare*. Benchtop instruments for sweat chemical analysis (e.g. high precision liquid chromatography (HPLC) and impedance-based spectroscopy) are being replaced by on-the-go wearable sensors with various colorimetric and electrochemical assays integrated on a single platform. The reduction in size and cost of sensor platforms is achieved by using polymeric elastomers, smart adhesives, and flexible printed circuit boards with on-board electronics. Smartphones have become the computing device of choice to capture digital images under varied lighting conditions, quantify the biomarker concentrations in the assays, control the wireless transmission modules, and pass the data on to the cloud. The publication trend shows that data collection, handling, delivery, and storage is becoming seamless and user-centric with minimal or no user intervention. The recent thrust is to identify early warning signs

of health conditions (e.g. hydration levels, athletic performance, energy metabolism, metabolic alkalosis) using combinations of chemical biomarkers (e.g. levels of sodium, chloride, lactate in sweat) and physiological parameters (e.g. heart rate, respiration rate, blood oxygen levels, skin temperature) [7,13,18,40,66]. In the coming years, we anticipate the integrative fusion of physical and chemical domains, both from sensing and data collection regimes, to provide real-time and continuous feedback on health metrics for the end user.

11. Conclusion

Wearable sweat sensors offer the possibility of non-invasive, real-time, on-the-spot biochemical analysis. Two broad areas of sweat sensing applications are fitness/high performance sports and disease diagnostics/healthcare. Key biomarkers for wearable sweat sensors are pH and electrolytes (for hydration monitoring), glucose (for diabetes prevention and management), sodium and chloride (for cystic fibrosis diagnosis), alcohol (for sobriety), lactate (for sweat gland metabolism), urea/creatinine (for renal functions), and trace elements (for illicit drug testing). Wearable sweat sensors employ various strategies for sweat production, collection, storage, and analysis. Sweat production is triggered by physical exercise (e.g. cycling, running, swimming, skipping, burpee test), thermal stimuli (e.g. sauna, foot bath) or localized electrical stimulation (e.g. iontophoresis using pilocarpine). Sweat collection and storage is accomplished with absorbing pads, commercial sweat collectors or microfluidic channels in paper or polymer. Sweat analysis is largely dependent on the biomarker under test and has been performed using potentiometry, amperometry, voltammetry or colorimetry. Wearable sweat sensors are often tested for their stability, shelf life, mechanical strength, calibration requirements, detection limits, response time, power dissipation, biocompatibility, and resilience to harsh environments. Better energy sources for powering these devices are being developed within the realm of lithium-ion batteries, energy harvesting devices, and supercapacitors. Most wearable sweat sensors use wireless data communication (e.g. Bluetooth or near-field communication) with custom smartphone applications to display the analyzed data to the user. There is considerable interest in commercializing wearable sweat sensors, and a number of established companies (e.g. in skin care products, hydration drinks, fitness equipment, and automobiles) have infused competitiveness in this area. We have highlighted some exemplary wearable sweat sensors which incorporate features of multi-functionality, on-body compliance, and system integration on flexible substrates. Future challenges in wearable sweat sensing are associated with continuous sweat collection and monitoring, variations in sweat production rates across populations/settings, mapping of spatial and temporal fluctuations in sweat biomarker levels, calibration with blood samples, identification of new (or more appropriate) sweat biomarkers, improved data communication for longer life and reusability, leveraging Big Data and smart analytics, skin biocompatibility studies, clinical validation in the field, and market adoption strategies with enhanced user experience.

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Biographies

Christopher Legner obtained his BS in Physics and Chemistry at Illinois State University in Bloomington Normal, Illinois. He has since moved to Ames, Iowa, where he is currently in his 4th year of graduate study at Iowa State University where he has spent time working for Santosh Pandey. His primary research focus has been on the development of automated instrumentation systems.

Upender Kalwa obtained his BA in electrical engineering from JNTUH, India. He was born and raised in India. Before starting his PhD, he worked for two years as a systems engineer in Tata Consultancy Services, India. He is currently in the fourth year of his PhD in electrical engineering at ISU. His work is centered on developing computer vision / image processing algorithms, and data analysis for health diagnostic devices used in the lab.

Vishal Patel is an undergraduate student in Electrical and Computer Engineering at Iowa State University with interests in embedded systems and integrated circuit design. In our group, he has developed skills in programming firmware for Bluetooth sensors and designing printed sensor circuit boards.

Austin Chesmore is an undergraduate student in Electrical and Computer Engineering at Iowa State University. He has interest and project experience in integrating machine learning / deep learning into control systems. His recent projects have mostly involved the fields of human computer interaction (HCI) as well as the optimization of integrated sensor systems.

Santosh Pandey is an Associate Professor in Electrical and Computer Engineering at Iowa State University. His group has interests in the design and development of novel sensors and instrumentation for biological applications. We have worked on microfluidic devices and electronic systems for automation, cost reduction, portability, and increased throughput within the broad areas of plant pathology and veterinary medicine.