Wearable sweat sensing for prolonged, semicontinuous, and nonobtrusive health monitoring

Emma J.M. Moonen MSc¹,²  |  Jelte R. Haakma MSc³  |  Elisabetta Peri PhD³  |  Eduard Pelssers PhD¹,⁴  |  Massimo Mischi PhD³  |  Jaap M.J. den Toonder PhD¹,²

¹ Department of Mechanical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands
² Institute for Complex Molecular Systems (ICMS), Eindhoven University of Technology, Eindhoven, The Netherlands
³ Department of Electrical Engineering, Laboratory of Biomedical Diagnostics, Eindhoven University of Technology, Eindhoven, The Netherlands
⁴ Philips Research, Royal Philips, High Tech Campus, Eindhoven, The Netherlands

Correspondence
Jaap M.J. den Toonder, Department of Mechanical Engineering, Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands.
Email: j.m.j.d.toonder@tue.nl

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Abstract
Together with the upcoming market for wearable consumer technologies, noninvasive and continuous health monitoring has become a new trend in the healthcare landscape. In recent years, significant research has been targeted toward the development of wearable sensing devices for monitoring biomarker levels in nonobtrusively accessible biofluids such as tears, urine, saliva, and sweat. Sweat could be an ideal candidate for prolonged, semicontinuous, and nonobtrusive health monitoring because sweat is a continuously accessible biofluid containing physiologically and metabolically rich information. However, challenges still remain toward commercialized wearable sweat-sensing devices, and the correlation between biomarker concentrations in sweat with health conditions still seems to be not fully understood. This review article aims to display the full scope of sweat sensing for health monitoring, starting from the fundamentals of human sweat, via modeling of the sweat gland physiology toward wearable sweat-sensing devices in research and commercialization efforts. Finally, the challenges of sweat sensing that still have to be overcome toward the utilization of sweat sensing in the conventional healthcare settings are discussed.

KEYWORDS
modeling, monitoring, sensors, sweat, wearable

1 INTRODUCTION

In medicine, monitoring is the careful observation of a patient for a period of time to track the progress or deterioration of an individual’s health status. The conventional case of health monitoring in the hospital utilizes a patient monitor to record and display the vital signs of patients. Sensors, for example ECG-leads, SpO₂ sensors, and blood pressure cuffs, record vital signs and transmit them by wire to a conventional stationary monitor or smaller battery-powered mobile monitor. The monitor readouts can be combined with sampling of blood for the detection of concentration of additional biomarkers such as partial oxygen, carbon dioxide pressure, electrolyte, glucose, and lactate. The blood samples are analyzed in the intensive care unit (ICU) or transferred to a centralized laboratory.
for analysis. Sample frequency can be a number of minutes to once a day, strongly depending on the illness and the health status of a patient. This sampling method inherently leads to discrete monitoring and does not allow for the continuous monitoring of patients. Especially in critical situations, this hampers a timely detection of life-threatening conditions.

In recent years, an increasing number of publications on the development of wearable medical devices for monitoring biomarkers in nonobtrusively accessible biofluids such as tears, sweat, urine, or saliva can be observed. Wearable sensors are being adapted to facilitate noninvasive or minimally invasive, continuous and low-cost testing outside the hospital setting. Health monitoring is extended from patients in healthcare settings toward athletes and laborers. Current commercially available wearable devices, for example, smartwatches, activity trackers, and smartphone apps, monitor activity levels already integrated with the heart rate. It can be foreseen that in the future additional vital signs combined with chemical biomarker sensing will be integrated as well. Each of the aforementioned nonobtrusively accessible biofluids poses challenges for wearable sensing applications. Sampling of tears can cause discomfort or irritation in the eye. Although urine can be accessed with minimal invasiveness, it needs to be drawn from the patient at fixed time slots, like blood, and is therefore unsuitable for continuous measurements. When continuous urine sampling is required, a catheter needs to be used, which is no longer classified as noninvasive. Reliable sensing of biomarker levels from saliva is challenging as the composition of saliva is highly linked to the last meal of the patient. Furthermore, a correlation to the biomarker levels in blood, the gold standard in health monitoring, is often unknown. While sweat sensing comes with its own challenges, it is seen as an ideal candidate for prolonged semicontinuous monitoring of biomarkers, because sweat is a continuously accessible biofluid containing physiologically and metabolically rich information. This information might be used to predict biomarker levels in blood or to infer pathologies directly. Sweat sensors can be placed on the skin, that is, in close proximity to the sweat-generation site, allowing for fully wearable devices, fast noninvasive measurements, and minimal sample degradation.

Interest in the field of sweat sensing started in the 1950s. More recently, together with the upcoming market for wearable consumer technologies, wearable sweat-sensing devices are receiving an increased research interest. A search in the Web of Science database for the search terms ("sweat" or "perspiration") and ("sensing" or "sensor" or "detection") yielded as little as 2 publications published in 2009 and 55 published in 2019, evidencing a rapidly increasing interest in the topic.

In this review, we provide an overview of the current wearable sweat sensors systems for prolonged, semicontinuous, and nonobtrusive health monitoring. To be able to develop sweat-sensing technology, a basic understanding of the mechanisms of sweat is necessary. Therefore, the first section of this reviews summarizes the fundamentals of human sweat, including the composition of eccrine sweat and the secretion mechanisms. Next section provides an overview of the models designed for connecting chemical biomarker levels in sweat to clinically relevant conclusions, for example via blood biomarkers. Current sweat-sensing technologies and platforms are then reviewed, with a distinction being made between sensing devices in research on the one hand, and efforts toward commercialization of the sensing platforms on the other hand. Lastly, the review will discuss the challenges that still need to be overcome to enable sweat sensing in the conventional healthcare settings.

## 2 FUNDAMENTALS OF HUMAN SWEAT

Sweat is an analyte-rich fluid secreted by sweat glands onto the human skin and plays an important role in the thermoregulation of the body. Other possible functions of sweat are the inhibition of bacterial growth, and moisturizing the skin. Humans are born with about 1.6–5 million sweat glands distributed all over the body with an average density of 200 glands/cm². These sweat glands can be classified into two categories, eccrine and apocrine, and in the literature there is debate on even a third category being apoeccrine glands. While eccrine sweat glands appear over the whole body except for the lips, the nail bed, and parts of the genitals; apocrine and apoeccrine glands are only present at limited body sites with hair, such as scalp, axilla, and genitals, and are excreting into the hair shaft. Due to the production of sebum by the sebaceous glands that also excrete into the hair shaft, the apocrine and apoeccrine sweat becomes a complex and viscous mixture of lipids, proteins, and steroids. Furthermore, because these hairy body sites are not convenient sampling locations, apocrine and apoeccrine sweat is not a preferred sampling fluid for wearable sweat-sensor technologies. For these reasons, this review will focus on eccrine sweat only.

The average eccrine sweat gland density over the whole body was found to be 200 glands/cm² with a maximum of about 500–600 glands/cm² on fingertips and toes. As schematically shown on the left in Figure 1A, the eccrine sweat gland consists of three main parts: the secretory coil, the dermal duct, and the upper coiled...
FIGURE 1  (A) Anatomy of an eccrine sweat gland. The eccrine sweat gland consists of three parts: the secretory coil, the dermal duct, and the upper coiled duct. The length of the total gland is typically 4–7 mm. (B) Half cross-section of the secretory coil and (C) the dermal duct. Mechanisms of sweat secretion at cell level are depicted with the arrows, the solid lines depict active transport, the dotted lines passive diffusion, and the dashed lines facilitated diffusion. The numbers refer to sequential events during sweat production, as discussed in the text.

duct or acrosyringium.9,11 The length of the total gland is typically 4–7 mm and the opening of the sweat gland to the skin surface has an inner diameter of 20–60 µm.9 However, the dimensions differ significantly between individuals of different sex, ethnicity, and age.18,20

This article will give an overview of the fundamentals of human sweat, including mechanisms of sweat production, secretion rate, sweat induction, and eccrine sweat composition.

2.1 Mechanisms of Sweat Production

Sweat production in eccrine sweat glands is controlled by the nervous system.13 Several external triggers can stimulate parts of neuronal centers to release nerve stimulants to the sweat glands resulting in an increase or decrease of activity, as explained in Section 2.3. The basic mechanism of eccrine sweat production is based on the Na⁺-K⁺-2Cl⁻ cotransport model.11,13 Na⁺-K⁺-2Cl⁻ cotransporters are electroneutral ion transport proteins that play an important role in cell ion homeostasis, volume control, and mediation of movement of ions and water across epithelia.21 The first step in sweat production is the secretion of proto-sweat in the lumen of the secretory coil, subsequently this proto-sweat passes through the duct and is secreted as sweat on the skin.9,11 As displayed in Figure 1B, proto-sweat is excreted by the cells in the secretory coil in a sequence of the following steps:

1. Upon an external trigger, the nervous system stimulates the nerve endings around the sweat glands to release a neurotransmitter.13
2. Binding of this neurotransmitter to the clear cell triggers an influx of Ca²⁺ into the intracellular fluid of the clear cells from both intracellular storage and interstitial fluid (ISF).11,13 Without this Ca²⁺ influx no sweat production can occur.22
3. The influx of Ca²⁺ appears to lead to the opening of K⁺ channels,13 which leads to an efflux of K⁺ from the cell to the ISF, and an efflux of Cl⁻ via facilitated diffusion to the lumen.11,13 Facilitated diffusion is the spontaneous passive transport of a chemical via integral transmembrane molecules.23
4. The efflux of $K^+$ and $Cl^-$ from the cell makes the cell hypotonic to the ISF and lumen, which causes an outflow of water from the cell. Aquaporin, that is water channels, facilitate the flow of water toward the lumen. Due to this efflux of water, the cell shrinks.\footnote{11}

5. The efflux of $K^+$ and $Cl^-$ also lowers the $K^+$ and $Cl^-$ gradients that the Na$^+$-$K^+$-2Cl$^-$ cotransporters have to overcome thus creating the Na$^+$ gradient by the Na$^+$-K-ATPase. This lead to an electrically neutral influx of Na$^+$, $K^+$, and $Cl^-$ into the cell.\footnote{13}

6. Subsequently, Na$^+$ is actively transported out of the clear cell toward the ISF via Na-K-ATPase,\footnote{11} leading to the active transport of $K^+$ into the cell. The $K^+$ ions can leave the cell on the basolateral side, that is the side oriented away from the lumen, through the opened $K^+$-channels via facilitated diffusion.\footnote{11,13}

7. Furthermore, $Cl^-$ passive transport from the clear cell toward the lumen is facilitated via $Cl^-$ channels through the apical membrane, that is the plasma membrane that faces inward to the lumen.

8. Increased $Cl^-$ concentration in the lumen creates an electrochemical gradient for Na$^+$ movement across the cell junctions from the ISF to the lumen.

9. This inflow of Na$^+$ and $Cl^-$ makes the lumen hypertonic to the ISF, which causes water to flow from the clear cells into the lumen and restore equilibrium. Once the calcium concentration in the cytosol of the clear cells decreases, the production of proto-sweat pauses and the clear cells swell to their original size.\footnote{22,24} This process of proto-sweat production is powerful enough to create enough pressure to force the sweat through the duct and onto the skin.\footnote{9} Early publications show a maximum hydrostatic pressure of up to 70 kPa.\footnote{25,26} However, additional publications of experimental studies proving this high pressure cannot be found in the literature. A more recent study found average values of secretory fluidic pressures generated at the surface of the skin by eccrine sweat glands in healthy young adults are between 2.4 and 2.9 kPa, which is much lower than the earlier research found.\footnote{27}

During passage of the sweat through the duct, the concentration of the electrolytes Na$^+$, $Cl^-$, and $H^+$ can change as a result of ion reabsorption by the luminal cells in the duct. The rate of this reabsorption is influenced by the sweat rate and therefore these electrolyte concentrations in excreted sweat are usually sweat rate dependent. The reabsorption process in the sweat gland duct at cell level is displayed in Figure 1C, and follows the sequence hereafter:

10. The wall of the duct consists of two layers of cells. They are referred to as the luminal and the basal cells. It is assumed that these two layers are connected via gap junctions.\footnote{28} In the basal cells Na$^+$ is actively transported into the ISF via the Na-K-ATPase. This leads to a low Na$^+$ concentration in the basal cells, and due to the gap junctions the concentration of Na$^+$ is lower inside the luminal cell than in the duct. The $K^+$ ions can leave the cell on the basolateral side via the opened $K^+$ channels, thus by facilitated diffusion, into the ISF.\footnote{11}

11. This gradient drives the facilitated diffusion of Na$^+$ from the proto-sweat into the luminal cell.

12. The removal of Na$^+$ from the proto-sweat provides the electrical energy to let $Cl^-$ out of the proto-sweat via passive diffusion through the cystic fibrosis membrane channel into the luminal cells of the duct and toward the ISF.\footnote{11} Most of the NaCl removal occurs in the lower part of the dermal duct.\footnote{11}

13. It is also possible that the sweat duct absorbs bicarbonate from the produced sweat. However, the specific mechanism for this process is not fully understood.\footnote{11,22}

## 2.2 | The Pulsatile Nature of Sweating

Multiple independent studies confirm that sweat secretion has a pulsatile nature.\footnote{9,22,29–37} The frequency of sweat expulsions is dependent on several factors, both internal and external.\footnote{29} Expulsions of active sweat glands occur synchronously over the general body area and the frequency of these expulsions is controlled by the nervous system.\footnote{30} The local sweat rate is linearly dependent on the expulsion frequency, and in thermal equilibrium the expulsion frequency is linearly, but not exclusively, related to the ambient temperature.\footnote{29} Whether the expulsions are caused by peristaltic/contracting movement of the coil or a pulsatile sweat production,\footnote{36} or both, is yet to be discovered.\footnote{22,29,38}

## 2.3 | Sweat Rate

Humans have widely variable sweat secretion rates, ranging between 0.02 and 20 nL/min/gland.\footnote{39,40} In sedentary state, individuals have a very low sweat rate of 0.02–0.3 nL/min/gland.\footnote{41,42} The total accumulated sweat rate is partially dependent on the number of active sweat glands, as not all sweat glands are active at the same time.\footnote{30} The sweat production is controlled via the so-called central and peripheral control; the hypothalamus provides the central control of the sweat rate, while factors associated to a sweat gland, such as size, temperature and osmolarity, influence the peripheral control for that sweat gland. Central control influences the expulsion frequency and the number of active glands via the nerves; as central control operates via nerve impulses, the expulsion frequency
can be measured using microelectrodes. Peripheral control changes the amount of sweat excreted per gland per expulsion. The amount of sweat secreted per sweat expulsion will later be referred to as the amplitude.

Although multiple factors that influence local and/or central control have been found in the past, mostly by studying the expulsion frequency and the accompanying amplitude, a lot remains to be discovered and confirmed. The most dominant factor for an increase in sweat rate is the average whole-body temperature. A higher body temperature leads to upregulation of central control, which increases the pulse frequency of the sweat glands, thus increasing the sweat rate and allowing greater heat dissipation. Furthermore, increases in local skin temperature can also have an effect on the local sweat rate. As opposed to increases in body temperature, local skin temperature only has an influence on the peripheral control and thus leads to an increase in the amount of sweat excreted per expulsion. Acclimatization to temperatures may, in the long run, decrease the expulsion frequency and lead to an increase of the amplitude. Another factor for changes in sweat rate is activity level. Exercising leads to an increase in expulsion frequency. Thermoregulation during exercise is very important; however, sweating will start before body temperature rises. Hyper- or hypoxemia, that is dehydration or hydration levels, has impact on the central control of the sweat gland activity, altering the pulse frequency. Abnormal levels of carbon dioxide in the blood, that is hypo- or hypercapnia, lead to changes in sweat production in terms of both expulsion frequency and amplitude; elevated levels of carbon dioxide lead to upregulation of sweat rate, while decreased levels lead to a decreased sweat rate. Furthermore, hypo- or hypercapnia generally alters the body temperature leading to a response from the central nervous system. Local hypoxia, that is oxygen deprivation, in the tissue surrounding the sweat glands will lead to a decrease in sweat expulsion amplitude. Emotion can also have an effect on the sweat rate. Emotional sweating as a result of stimuli such as stress, pain, or anxiety occurs over the whole body, but is more evident at palms and soles of the feet, primarily due to the high sweat gland density at these body sites. Finally, the biological gender of the subjects can have an influence on the sweat rate. However, these differences have been proven only under specific circumstances.

2.4 Sweat Induction

A sufficient amount of sweat is usually necessary for wearable sweat sensors to perform optimally. Depending on the use case and the design of the device, sweating needs to be induced in order to be able to collect and transport enough sweat into the wearable sweat-sensing device toward a sensor for measurement of chemical biomarker levels. Different methods of sweat induction can lead to different sweat compositions, and this should be taken into account in the interpretation of the results from the sweat-sensing system. There are generally three methods used in the field of wearable sweat sensing to induce sweat. The first method is pharmacological, by iontophoretic delivery of nerve stimulants, such as acetylcholine, carbachol, bethanechol, or pilocarpine, to the sweat glands. Second, sweat can be induced by passive thermal stress. Sweat is induced by placing subjects in a climate room with elevated temperature, or by applying local heat to the skin. Finally sweat can be induced by physical activity, for example exercise. As already anticipated, increased levels of physical activity lead to an increased sweat rate.

2.5 Eccrine Sweat Composition

Human eccrine sweat is a slightly acidic fluid with common pH values ranging between 4.0 and 6.0 and is composed mainly of water (99%). It contains a wide variety of chemical components, some of which may be used as biomarkers. Table 1 provides an overview of the most important analytes present in sweat for health monitoring, with indications of typical concentrations and their possible link with health/disease conditions. Some of these links to health are evident with respect to blood biomarkers, but it might not be possible to prove the link with sweat biomarkers. While most biomarkers partition from blood to enter into ISF and subsequently to sweat, some chemical components of sweat can also originate from the sweat gland cells. For many components the mechanism by which they enter the sweat is unknown. Furthermore, the concentration of some chemical components in sweat are sweat rate dependent, including electrolytes that can be reabsorbed by the sweat gland duct, that is H\(^+\), HCO_3^-, Na\(^+\), and Cl\(^-\), as well as metabolites such as lactate that are produced by the sweat gland cells themselves depending on the metabolic activity.

Examples of how certain biomarkers enter the sweat include: chloride that is being secreted into the sweat by the clear cells, sodium that can diffuse between the cells of the coil, and ammonium that likely diffuses through the clear cell apical membrane as ammonia. Lactate is secreted by the clear cells into the sweat; however, it is not fully understood whether entire lactate originates from the metabolism of the sweat gland cells or whether it partitions from blood via the ISF into the sweat as well. Ethanol is capable of diffusing through membranes, and...
### TABLE 1  Common components of sweat, with indications of typical concentrations and their link with health/disease conditions

| Analyte          | Concentration | Link with health                                           | References |
|------------------|---------------|-----------------------------------------------------------|------------|
| **Electrolytes** |               |                                                           |            |
| Sodium ($Na^+$)  | 10–90 mM      | Dehydration, cystic fibrosis                              | 9,17,52–58 |
| Chloride ($Cl^-$)| 10–100 mM     | Dehydration, cystic fibrosis                              | 9,17,59,53,58,60 |
| Ammonium ($NH_4^+$)| 0.5–8 mM   | Hepatic disorders, protein catabolism                      | 9,61,58    |
| Potassium ($K^+$)| 1–24 mM       | Renal failure, insulin deficiency, adrenal deficiency      | 9,17,62,63 |
| Calcium ($Ca^{2+}$)| 0.5–3 mM   | PHT disorders, gram-negative sepsis                       | 50,64–66   |
| **Trace metals** |               |                                                           |            |
| Zinc             | 275 µg/L      | Excess Zinc                                               | 10,67      |
| Cadmium          | <100 µg/L     | Toxic metal exposure                                       | 10,68,67   |
| Lead             | <100 µg/L     | Toxic metal exposure                                       | 10,68,67   |
| Mercury          | 0.1–1.4 µg/L  | Toxic metal exposure                                       | 10,68,67   |
| Copper           | 250 µg/L      | Copper deficiency                                          | 11         |
| Magnesium        | 0.02–0.40 mM  | Magnesium deficiency                                       | 11         |
| **Cytokines**    |               |                                                           |            |
| IL-1α            | 3.7–13.6 pg/mL| Inflammation marker                                       | 69,70      |
| IL-1β            | 6.9–18.4 pg/mL| Inflammation marker                                       | 69,70      |
| IL-6             | 0.15–5.5 pg/mL| Inflammation marker                                       | 69–72      |
| IL-8             | 1.5–6.1 pg/mL | Inflammation marker                                       | 69,70      |
| IL-10            | 0.048–0.124 pg/mL| Antiinflammation marker                       | 72         |
| TNFα             | 9.3–21.2 pg/mL| Inflammation marker                                       | 69,70,72   |
| TNFβ             | 1.7–6.2 pg/mL | Inflammation marker                                       | 69         |
| **Organic components** |       |                                                           |            |
| Lactate          | 6–60 mM       | Anaerobic catabolism, inhibits bacterial growth, sepsis marker, pressure ischemia | 9,10,73,59,63,74–77 |
| Glucose          | 0.05–0.2 mM   | Diabetes, shock (stress hyperglycemia)                     | 9,11,14,73,78,59,79–85 |
| Ethanol          | 2.5–22.5 mM   | Inebriation                                               | 9,86,87    |
| Urea             | 2–12 mM       | Kidney failure marker                                     | 9,11,88,78,89 |
| Cortisol         | 0.10–25.00 ng/mL| Stress marker                                              | 90         |

Other lipid-soluble molecules can also enter the sweat via diffusion through the cell membranes. In the proto-sweat the concentration of $K^+$ is similar to that in the blood, while in the excreted sweat the concentration of potassium is significantly higher than in blood. Although the transport mechanism of $K^+$ into the proto-sweat is documented, the fact that $K^+$ concentration is higher in excreted sweat with respect to proto-sweat is not well understood. It has been suggested that $K^+$ transports through the duct into the proto-sweat rendering excreted sweat of high $K^+$ concentration. Urea is another example of a component of sweat for which it is uncertain how it enters the sweat. There exist theories and models on urea transporters and production by the sweat gland cells, however no conclusive answer can be given on the origin of urea concentration in sweat. Cytokines are found in such low quantities that there is still a debate on whether they are a true part of sweat or a contamination from the skin. Of other chemical components of sweat, for example heavy metals and glucose, the mechanism by which they enter the sweat is still unknown.

### 3  MODELLING THE SWEAT GLAND FUNCTION

Most nonbiological complex systems consist of many simple and identical components. In contrast, biological systems, such as cells, tissues, and organs, consist of many diverse components that are often multifunctional. This makes it challenging to obtain a complete and intuitive understanding of biological systems. In this context, modeling is needed to provide a simplified and quantitative interpretation of interactions and to predict response to external stimuli or system dysfunctions.

Many experimental attempts have been made to correlate the sweat biomarkers to blood concentration. For only a few biomarkers, for example ethanol and arsenic, this
correlation has been found.\textsuperscript{11,68} This limits the ability of the clinic to utilize sweat biomarkers. Therefore, modeling the perspiration process is of relevance to foster the understanding of the related (patho)physiological processes and to translate the information from sweat biomarker concentrations into clinically relevant data. The design of a model to study the (patho)physiology of perspiration might enable the use of various biomarkers for noninvasive monitoring and diagnosis of different clinical conditions. Possible promising applications might be for diabetes (hypo-/hyperglycemia), delirium (stress hyperglycemia\textsuperscript{93}), sepsis (hypocalcemia,\textsuperscript{62,94} hyperlactemia\textsuperscript{95}), kidney failure/insufficiency (urea,\textsuperscript{88} potassium\textsuperscript{62}), and dehydration (hypo-/hyperglycemia), delirium (stress hyperglycemia\textsuperscript{93}), sepsis (hypocalcemia,\textsuperscript{62,94} hyperlactemia\textsuperscript{95}), kidney failure/insufficiency (urea,\textsuperscript{88} potassium\textsuperscript{62}), and dehydration (sodium\textsuperscript{62}). In the current state of the art, development in modeling is limited due to insufficient experimental data for reliable parameter estimation. In the future, various statistical methods, including a Bayesian approach,\textsuperscript{96} can be used to identify which physiological variable is the most interesting to investigate. There are many opportunities to gain new knowledge on sweat production through modeling, and it may enable further investigations in the field. The use of a model-based approach to investigate sweat is quite recent. To the best of our knowledge, only two studies have been proposed on sweat modeling.

Sonner et al. (2015) attempted to model perspiration with a mathematical approach. The sweat gland is described as a microfluidic transport system in a steady state.\textsuperscript{9} The steady-state assumption is made disregarding the pulsatile nature of sweat reduction. Figure 2B shows the proposed lumped component model for the sweat flow. The authors propose a description of the sweat flow in the sweat gland by its electrical equivalent. The partitioning rates of potassium, ammonia, urea, and ethanol from the blood to the proto-sweat were assumed fast enough for the concentrations to be sweat rate independent. For ammonia, a pH dependence is also reported. This mathematical description assumes the ammonia content in sweat to be equal to the ammonium content in plasma multiplied by a pH-dependent factor. How the pH influences this factor remains unknown. No validation of the models and mathematical expressions are discussed in this publication. As such, Sonner et al. provide the first groundwork upon which a more comprehensive model can be build.

La Count et al. (2019) reported progress on a physiology-based transport model of the sweat gland aimed at linking glucose in blood to glucose in sweat.\textsuperscript{97} The model, illustrated in Figure 2C, is a dynamic compartment model that includes the blood, ISF, aqueous boundary layer, collection coil, duct, and upper coiled duct. The model considers four electrolytes only (potassium, chloride, sodium, and bicarbonate).

The dynamic model was calibrated with one dataset from an experiment carried out by the authors, and three datasets derived from the literature. Of the four model parameters identified as relevant, two (dermal clearance constant and sweat rate) were measured experimentally and two (skin layer metabolic uptake and epithelial glucose permeability) were fitted to match simulation and experiments. Simulation results were consistent with three of the datasets. In the other dataset, the sweat rate was estimated instead of measured, possibly explaining the poor match.\textsuperscript{97} The model showed a 10-min blood-to-sweat lag and a 0.001–0.020 ratio between blood glucose and sweat glucose levels. This ratio is dependent on the sweat rate, but this relationship was not further described in the publication. The model demonstrates that sweat rate is an important factor in translating sweat glucose levels to blood glucose levels.

When constructing the model, La Count et al. took into account many factors that play a role in glucose transport and sweat generation. Yet other factors that may also influence the correlation between blood and sweat were not included, such as the increase in glucose demand when cells become more active. Therefore, future work should include model validation, preferably with newly obtained experimental data, to assess whether important factors were missed. Assessment of inter- and intrasubject variability should also be performed to estimate the generalizability of the model.

4 | STATE OF THE ART IN SWEAT-SENSING TECHNOLOGY

Recent years have shown increased research efforts on the development of wearable sweat-sensing platforms. Research groups around the globe are designing novel technologies that are incorporated into wearable devices for health monitoring of individuals. Furthermore, startups and established companies are bridging the gap between research and commercial solutions and bringing wearable sweat sensors to the market. A fully integrated wearable sweat sensor consists of many parts, which are all tailored to a specific use case, the main two components being the sweat collector and the sensor. The choice of the sweat-collection mechanism is usually based on the amount of sweat produced by the user. For example, a wearable sweat-sensing device intended for athletes should have sufficiently large volume and should be able to remove abundant sweat. Opposite to athletes are sedentary patients in the hospital; sweat-collection mechanisms in sweat-sensing devices for these users should incorporate techniques to collect minuscule amounts of sweat. Sensing technologies are widely studied and are also tailored to specific user groups. Most commonly electroanalytical techniques are used to detect analyte levels in sweat; the
FIGURE 2  Schematic microfluidic representation adapted from Sonner et al. (panel B). The sweat gland coil in the model of Sonner et al is modeled as a combination of voltage sources and resistors and used resistors exclusively to model the duct and the upper coiled duct. The resistance experienced by the sweat in the duct and the upper coiled duct are represented by resistors. Until the sweat droplet evaporates, the Laplace pressure inside the droplet provides a pressure against the sweat flow. This Laplace pressure is modeled as a voltage source ($P_L$). The coil has two aspects to it, the first is the resistance the sweat experiences as it travels through the coil ($R_s$), the second is the influx of sweat into the duct, which increases the flow through the coil. The sweat influx is represented by a pressure source ($P_l$), caused by the difference in osmotic pressure. Multiple resistors and voltage sources are needed to approximate the continuous increase in water flow through the coil. When drawing the electrical equivalent of the model, adjustment to grounding and configuration of coil pressure generators are needed. The model of La Count is depicted as a compartment model in panel C. The interactions between the compartments grouped under “other” are described with equations that differ per chemical and are not accurately described in terms of convection and/or diffusion. Not shown in the image is the glucose uptake by the cells in the “interstitial fluid (ISF) near capillary” compartment. Reprinted from Sonner et al.9 with the permission of AIP Publishing.

broad choice of specific methods within this category allows for a wide range of analytes and concentrations to be measured. Optical detection forms another category of techniques used in the field of wearable sensing technologies. A variety of dyes have been developed that react with different analytes in sweat, and the concentration of the analytes can be determined using various optical detection techniques. In the next section, we discuss the different techniques proposed for sweat collection and for sensing sweat components, as well as the integration of these techniques into wearable sweat-sensing devices.

4.1  Sweat Collection

Wearable sweat sensing starts with the collection of the test sample, that is, eccrine sweat. This sweat, originating from the eccrine sweat glands, is subsequently transported to the sensor to measure the concentration of the targeted analytes. A division into three main categories of sweat collection is made: (1) microfluidic collection that uses microfluidic architectures such as channels and chambers, (2) absorption collection by means of a wicking material to wick the sweat from the skin into the device, and (3) direct on-skin collection devices that use either a cavity in
the device or the volume created by the topography of the skin itself for the collection of sweat.

### 4.1.1 Microfluidic collection

Microfluidic techniques are most commonly used in wearable sweat-sensing devices to collect and transport small samples of sweat. Microfluidics refers to the confinement and precise control of micro/nanoliters of fluid at the small scale at which capillary forces govern the transport of mass. The designs of the microfluidic features can be straightforward and suitable fabrication techniques associated with it have been widely studied. Fabrication techniques vary from soft lithography to laser machining and mass production using molding. The reported microfluidics-based approaches for sweat collection have a large volume that exists between the sweat gland and the sensor, which can range between 10 and 20 µL. After filling the dead volume between the sweat gland and the opening in the device, which is created because of the roughness of the skin, the sweat needs to fill channels and/or reaction chambers, before the analyte concentration can be measured. This does not only hinder a fast detection but can also result in diffusion of analytes throughout the fluid in the channels, which will result in less accurate time-resolved measurement. The inherently larger volumes imply that fast and accurate detection can only be achieved at a higher sweat rate, in the order of tens of nanoliters per minute per gland to obtain sensor response times of 10–20 min. These high sweat rates make microfluidic techniques applicable, for example, for athlete monitoring, but less suitable for sedentary patients monitoring where sweat rates in the order of 0.1–1 nL/min/gland are more common.

Figure 3 shows examples of wearable sweat sensors that utilize microfluidic techniques to collect and transport sweat toward the sensing mechanism. Figure 3A depicts a recently developed microfluidic sweat sensor platform. The microfluidic structure in this device is entirely laser machined from polyethylene terephthalate (PET) and medical grade adhesives to facilitate scalable manufacturing. It is able to monitor uric acid and tyrosine concentrations by collecting sweat samples from exercising individuals into a multiinlet microfluidic module. With 10 inlets and an experimentally measured flow rate of 1.5 µL/min, the refreshing time to reach 90% of the new analyte concentration is in the order of 2–3 min, for a change in analyte concentration from 20 µM to 80 µM.

Figure 3B shows an example of a microfluidic device designed for sensing the sweat rate by determining the position of the sweat flow front in time. As a result of the pressure generated by the sweat glands, a serpentine microfluidic polydimethylsiloxane (PDMS) collection channel fills. The sweat in this channel passes multiple times over two interdigitated finger electrodes; those passages are recorded in time from which the sweat rate can be calculated. Microfluidic collection techniques are very well suited for sweat rate measurements, because of the relatively large volumes, while diffusion of analytes is not important for measuring sweat rate. However, the channel size of the device in Figure 3B is relatively large, having a cross-section of 100,000 µm². The lowest measured sweat rate reported with this device is 0.5 µL/min, thus it is applicable only to physically active or heat-stressed persons.

Figure 3C shows a device that, in contrast with most other published concepts, utilizes a vertical instead of horizontal microfluidic layout. The PDMS sweat collector was fabricated using a 3D printed mold and contains a conductivity sensor. Unfortunately, the initial volume of sweat necessary to reach the sensor is 5.6 µL, and therefore this device can only be used on individuals with a high sweat rate such as exercising or heat-stressed persons.

Instead of using capillary forces, the device shown in Figure 3D uses gravitational forces to collect a sweat sample for analysis. The design is based on a sweatband; during exercise the sensor is placed on the forehead, sweat drips into the device and then passes over an electrochemical sensor for the detection of Na⁺ concentration.

Figure 3E shows a microfluidic device for the detection of glucose and lactate in sweat from exercising individuals. Four collection chambers are placed on the skin and when enough sweat is present in these chambers, because of capillary forces, the sweat transports toward the sensing electrodes. The initial volume of the device is 8.72 µL which took 13.4 min to fill; therefore, the operating sweat rate of the device was experimentally estimated by the authors as 0.04 µL/min/gland.

The longer filling time of microfluidic devices can also be used as an advantage. For example, Figure 3F shows a device that uses capillary-bursting valves to fill certain reservoirs at fixed times for the analysis of temporal variations in electrolyte balance and biomarker concentrations. This device is used for capturing and storage of sweat, whereas processing and sensing is performed after removing the patch from the skin. The research group has been continuing the development and has incorporated colorimetric sensors in the patch. Further development of the patch could provide a fully wearable novel sweat-sensing platform.

In conclusion, microfluidic methods are widely used for the collection and transport of eccrine sweat. Attempts have been made to decrease the sample volume to accommodate lower sweat rates, however no devices suitable for monitoring sedentary individuals were found in the literature. Advantages of using microfluidic devices
are the availability of suitable materials and fabrication techniques to develop a flexible, wearable sweat-sensing device. Flexibility is important in order for the wearable device to conform with the skin for optimal adherence and minimal discomfort for the test subject.

4.1.2 Absorption collection

An absorbing material can be used to provide an improved sample collection by wicking sweat from the skin into the device. Absorption techniques can be especially useful when the users of the wearable sensors are sedentary and thus do not sweat enough for microfluidic devices to be effective, or when a fast sample collection is required. An absorbing material can be placed on the skin to wick sweat from the skin into the device, or downstream of the sensor to collect sensed sweat. A disadvantage of using an absorber on the skin is that the sweat is collected in a relatively large absorption pad before being led to the sensor, and therefore the measurements are averaged over larger volumes of sweat because the analytes diffuse throughout the material, and sweat collected earlier cannot be removed. Consequently, the measurement has a poor temporal resolution. Furthermore, contaminants from the skin can have a large influence on the measured results as they could also be taken up by the absorbing material. Figure 4 shows wearable sweat sensor devices
FIGURE 4 Wearable sweat-sensing devices that utilize absorption to collect and transport sweat into the device. (A) A microporous substrate is placed on the skin as a sweat absorption pad. Reprinted with permission [103]; Copyright 2014, Wiley. (B) This wearable sweat-sensing device optimally uses absorbing materials in the design of a conformable sweat sensor. Reprinted with permission [104]; Copyright 2018, Royal Society of Chemistry. (C) Control of the contact angle of the sweat on the material provides a way to transport the sweat toward the sensors. Reprinted with permission [105]; Copyright 2019, American Chemical Society. (D) Absorption pad, located at the skin side of the device, that uses geometrical features to wick the sweat from the skin into the device. At the end of the microchannel downstream of the sensors, a second absorbing material is placed to move sweat throughout the device, which acts as a waste reservoir at the same time. Reprinted with permission [106]; Copyright 2018, Royal Society of Chemistry. (E)(F) Examples of absorption collection using paper, paper is an excellent absorption material and commonly used in microfluidic wearable devices. Reprinted with permission [107,108]; Copyright 2016, Elsevier

that use absorption techniques to collect and/or transport sweat into or throughout the device.

The device in shown Figure 4A uses a microporous substrate as sweat-absorbing material. Five hydrophilic porous substrates have been tested as the sweat absorption materials, namely Whatman GB003 cellulose paper, Scotch-Brite recycle cellulose sponge, polyvinyl alcohol sponge, Kendall hydrophilic polyurethane foam dressing, and Mepilex silicone foam dressing. The final choice for the absorbing substrate has to be made taking into account the desired sensing modality, fabrication technique, and use case for the wearable sweat-sensing device.

The device in Figure 4B optimally uses absorption techniques in the design of a conformable wearable sweat sensor. Multiple absorption materials and shapes are used to optimize sweat collection to minimize sensor lag and to enable rapid removal of sweat from the sensing site to minimize effects on sweat physiology. The volume of the sensor flow cell is equal to 1.1 μL and will be refreshed within a minute at a medium sweat rate of 13 μL/cm²/h. This corresponds to a sweat rate of 2.1 nL/min/gland at a sweat gland density of 100 glands/cm², which is an order of magnitude lower than most sweat-sensing devices that use microfluidic collection and transport.

The device shown in Figure 4C uses control of contact angles of sweat on different materials for the specific absorption of sweat into the wearable sweat-sensing device. The smart combination of superhydrophilic-superhydrophobic sites enhances the sampling of sweat and improves the interface controllability between sensor patch and skin. A silica nanoparticle suspension was coated onto a PET film and employed as a superhydrophobic background, followed by oxygen plasma etching to define superhydrophilic microwells.

The device depicted in Figure 4D uses an absorption pad with a hexagonal microchannel structure that generates a capillary force that combined with the absorption force of a paper absorption pad placed after the sensor as a pump enables the continuous measurement of ethanol in sweat. Paper, or more specific hydrophilic cellulose or nitrocellulose fibers, is a commonly used absorption material in microfluidic devices, and a hydrophilic piece of paper is an excellent absorption material for sweat while the fabrication of such devices is straightforward.
Figure 4E shows a device with a sweat intake principle based on the use of paper. The device has an initial volume of 1.78 μL, which is approximately a 10-fold less compared to most microfluidics-based devices. The fluidic function of the paper within the device depends on the specific device design. In the device shown in Figure 4E, a filter paper is situated at the skin side of the device and absorbs the sweat directly from the skin. In the device depicted in Figure 4D, the paper is located at the end of the microfluidic channel and acts both as a pump and a waste reservoir. Figure 4F shows another wearable sweat-sensing device based on paper microfluidics. The paper structures have specific absorption rates for flow control: Whatman 4 paper has a fast absorption and is used for transport of sweat toward the sensor (red in Figure 4F), while high-capacity absorbing paper Whatman grade 113 pads are located at the terminal points of the channels to collect the analyzed sweat (dark gray in Figure 4F).

In conclusion, the integration of an absorbing material in a wearable sweat-sensing device can improve the collection of sweat over microfluidic approaches when sweat rates are low. Furthermore, absorbing materials can be used as a collecting waste reservoir of sweat that has passed the sensor. However, using absorbing materials can have an influence on the measured results as larger volumes rather than small discrete sweat volumes are collected, which are diffusively mixed in the absorbing materials before being led to the sensors.

4.1.3 Direct on-skin collection

Instead of designing a mechanism for the collection of sweat and subsequent transport to the sensors, the sensor can also be placed directly on the skin. In that case, either the sweat is collected within a cavity in the device situated directly on the skin, or the inherent roughness of the skin itself acts as a collecting structure. Figure 5 shows an overview of several wearable sweat-sensing concepts based on either of the mechanisms. A major advantage of collection and sensing directly on the skin is that no dedicated collection mechanism needs to be incorporated, which significantly simplifies fabrication and design. However, when sweat is not sampled but sensed directly on the skin, the skin topography and pH can interfere significantly with the measurement results. Furthermore, because there is no mechanism to actively remove the sweat from the sensor, analytes both from the sweat and the skin will diffuse throughout the measured volume and therefore the measurements will give global, averaged results. The device depicted in Figure 5A shows an example of a wearable sweat-sensing device containing a cavity with an integrated sensor for the collection and sensing of sweat on the skin. In the reservoir 20–30 μL of sweat need to be collected to ensure a stable and reliable analysis of heavy metal concentrations in sweat. Collection was performed on exercising individuals, and a sensor reading was obtained after 15 min. As sensed sweat is not removed from the sensing site, the measurements supply an average concentration over time because of the diffusion of the analytes throughout the sensing cavity. The electronic skin depicted in Figure 5B uses the cavities formed by the topography of the skin itself as a collection reservoir for sweat analysis. The device with electrodes is directly placed on the skin and therefore eliminates any requirements of sweat collection on or in the device. The authors do not specify a necessary amount of collected sweat; the device is placed on the arm or forehead during exercise, and after 8 min. of treadmill running the device is pressed onto the skin and a readout is given. Again
because this device has no sweat removal mechanism, the readouts are averages over time. Tattoo-like patches are a specific type of on-skin wearable sweat devices. Figure 5C shows such a tattoo-based device based on potentiometric sensing for monitoring ammonium in sweat.61 Tattoo-like patches are skin-worn sensors consisting of flexible electrodes printed on a temporary-transfer tattoo. Sweat is collected in the cavities of the skin underneath the electrodes, which inherently causes averaging of the measured results over time. This platform is ideally suited for applications in which subjects move much (e.g., in sports), because the sensor is flexible and can deform with the skin without tearing. However, this could also cause movement artifacts in the sensing results that have to be compensated in calibration or filtering.

In conclusion, on-skin wearable sweat-sensing devices in which the sensing element is in direct contact with or in close proximity of the skin can have a simple structure, and do not require complicated fabrication techniques for creating sweat-collection features on the device. However, the temporal resolution of the measured results is often poor.

4.1.4 | Other collection methods

Most wearable sweat-sensing devices currently developed use one of the aforementioned techniques for the collection of sweat samples. However, because every technique has its disadvantages, alternative collection techniques are also being investigated. One such novel method uses the principle of digital microfluidics, in which the sample is collected and further processed as droplets instead of a continuous flow of liquid. This discrete collection and transport has significant advantages over continuous processing because droplet sample volumes can be very small and diffusion of target molecules between droplets is inherently absent. Francis et al. developed a digital microfluidics-based sweat rate sensing device that can handle flow rates as low as 25 nL/min.109 The demonstrated device solely measures sweat rate by temporarily shorting droplets pinched off between two electrodes, after which the sweat droplets are collected in a wick for a possible further analysis. Noteworthy is that no sweat rate per gland can be determined without any assumption on the number of sweat glands per surface area. In addition, as a result of the collection of sweat droplets in the wicking material, time-resolved measurement will be difficult.

4.2 | Sensing Technologies

After collection and transport of a sweat sample, the desired analyte concentration in the sweat sample has to be measured. Table 2 provides an overview of the sensing techniques used in wearable sweat-sensing devices. Two distinct sensing categories used in wearable sweat-sensing devices can be defined: electroanalytical and optical methods.

4.2.1 | Electroanalytical

Electroanalytical methods, sometimes referred to as electrochemical methods, are a class of techniques that measure an analyte concentration by detecting the electrical potential and/or current in an electrochemical cell. In wearable sweat-sensing devices, flexible electrodes are often used that can comply with a possible movement and stretching of the devices. Electroanalytical methods can be divided into several categories based on which variables are controlled and are measured. Table 2 provides an overview of the electroanalytical sensing method categories; all references mentioned in this table refer to wearable sweat-sensing platforms where these techniques are incorporated. The first subcategory of electroanalytical sensing methods is chronoamperometry, which is widely used in wearable sweat-sensing devices for the detection of metabolites, such as lactate, glucose, uric acid, and ethanol. A fixed potential is applied to a sensing electrode and the current resulting from redox reactions is measured and related to the target analyte concentration. A major advantage of using chronoamperometry is the straightforward detection and the direct conversion of the current to a concentration. Furthermore, easy adaptations are possible to lower the necessary potential and thus the required power. However, typically a specific enzyme is used to provide selectivity for a certain analyte. Enzymes can be chemically inactivated as a result of byproducts of redox reactions or can even detach from the sensing membrane, which causes loss of signal and sensitivity. Immobilizing enzymes partially solves this problem, however chemically modifying the enzymes for immobilization can cause a reduction in activity.121

Potentiometry measures the potential between a sensing electrode and a reference electrode which are placed in contact with the sweat sample. Potentiometry is commonly used for the detection of sweat pH and electrolyte concentrations in sweat. It supplies a fast detection without the use of an enzyme and with minimal use of electronic components and processing.122 An ion-specific electrode is used to target specific ions. A major disadvantage of potentiometric sensing is that the analytes need to be charged to be able to measure their concentration. Therefore, potentiometry is not suitable for measuring metabolites, such as lactate and glucose, in sweat.
| Technique                              | Analytes                          | Advantages                                                                 | Disadvantages                                                                 | References     |
|---------------------------------------|-----------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------|
| **Electroanalytical**                 |                                   |                                                                            |                                                                                |                |
| Chronoamperometry                     | Metabolites: lactate, glucose, uric acid, ethanol, and urea | Simple detection and conversion of current to concentration. Easy adaptation to lower the necessary potential and thus minimize required power. | Usually requires an enzyme that has lower stability over time and a high sensitivity toward deviations in pH, temperature, and ionic strength. | 108,60,63,76,86 |
| Potentiometry                         | pH, electrolytes: Na⁺, K⁺, Ca²⁺, H⁺, NH₄⁺, Cl⁻ | Fast detection. Simple electronic detection scheme and processing.            | An ion-specific electrode needs to be developed to differentiate between different ions. The analytes need to be charged. | 50,52,104,61,79,55,56,110–113 |
| Voltammetry                           | Heavy metals: Cu, Zn, Pb, Cd, Hg    | One voltage scan on the same electrodes can be used to extract the concentration of multiple analytes. | More complex postprocessing is necessary | 98,67,114 |
| Electrochemical impedance spectroscopy| Cortisol, Interleukin-6            | Label-free method.                                                          | Longer analysis time. Sensitivity can be low. More complex postprocessing.     | 84,115 |
| Piezo-electricity                     | Metabolites: lactate, glucose, uric acid, and urea | No need for complex electronics. Self-powered                               | Devices can be fragile.                                                        | 78,116 |
| **Optical**                           |                                   |                                                                            |                                                                                |                |
| Colorimetry                           | Sweat rate, pH, metabolites, electrolytes | Can be operated without a power supply. Semiquantitative readout possible by visible inspection. Smartphone-based quantitative analysis possible | Nonuniformity of color can give deviations in the results. Stabilization of the color needs a longer sensing time. Not suited for continuous measurements. | 101,105,59,127,57,118,319 |
| Fluorometry                           | Chloride, zinc and sodium          | No power supply needed. Smartphone-based quantitative analyzing possible.   | Dark measurement setup necessary                                                | 120 |

Voltammetry deploys a voltage scan over sensing and reference electrodes, and the resulting current features can be used to extract the concentrations of multiple analytes in one scan. Usually voltammetry is used to characterize the sensors, however it can also be used to detect analytes such as heavy metals in wearable sweat-sensing devices. Comparatively, compared to chronoamperometry it requires more complex postprocessing to extract the peaks of different analytes from the scanning data.

Electrochemical impedance spectroscopy applies a sinusoidal electrical potential over the sweat sample, and the resulting current is measured to reflect the amount of binding of a target analyte on the sensor surface, which indicates the concentration. An advantage of this technique over the aforementioned techniques is that it does not require chemical labels as the binding of the analyte to the sensor surface produces the impedance change. A disadvantage of this technique is that it requires even more complicated postprocessing than voltammetry techniques and furthermore the sensitivity toward binding of the analyte to the sensor surface can be low.

The final electroanalytical subcategory that has been applied in wearable sweat-sensing devices is formed by piezoelectric methods. This less used sensing method is based on a piezo-enzymatic-reaction coupling process; binding of molecules on a piezoelectric material surface can change the surface carrier density, which thereby changes the piezo-screening effect and thus affects the piezoelectric output. Under the deformation of the device it produces an output voltage that can be significantly influenced by the analyte concentration in the sweat sample. Therefore, the piezoelectric output can be regarded as both the sensing signal and the electric power for driving the device. No external power supply is needed, as these wearable sweat sensors are self-powered by the movement of the users. Electroanalytical sensing techniques thus
all need the incorporation of electrodes into the wearable sweat sensor. Depending on the use and design of the sensor, these electrodes vary in size from several square micrometers to tens of square millimeters. A wide variety of materials for fabrication of (flexible) electrodes is available, from metals, such as gold and chromium, to conducting polymers, such as poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS). Furthermore, a power source, signal amplifiers, and signal processing parts usually need to be integrated on or (wirelessly) connected to the wearable devices.

In conclusion, electroanalytical methods are widely used in wearable sweat-sensing devices. The methods are easily adaptable toward the desired requirements and they can be designed and fabricated as flexible electronics to suit the wearable format. As power is usually necessary to operate these devices, clever electronic circuits need to be designed in order to keep the power requirement low to eliminate the need for a nonwearable power supply.

4.2.2 Optical

The second category of sensing methods used in wearable sweat-sensing devices are optical techniques. These can be divided into the subcategories of colorimetry and fluorometry. Both colorimetry and fluorometry use a dye that makes contact with the sweat and will change color or fluorescence upon binding with a target analyte. Optical techniques are employed for the detection of a wide variety of analytes, as indicated in Table 2. Fabrication and design of wearable sweat sensors using optical techniques is relatively straightforward. Typically, the color or fluorescence of a detection site of tenths of millimeters squared needs to be analyzed. While a qualitative analysis might be possible with the eye, a quantitative analysis would require a secondary detection device that captures and analyses the transmitted illumination. A smartphone can be used as a secondary device for the quantitative analysis as it contains a camera, wireless communication, and enough process power. However, because smartphone technology is rapidly evolving and major differences exist between different models, a dedicated readout device could also be designed. While a separate detection device does not qualify as a fully wearable device, it is an advantage as no electronics need to be incorporated in the on-skin device, as opposed to the electroanalytical sensing techniques where electrodes need to be integrated. Furthermore, optical techniques are difficult to use for continuous measurements, because the dyes are usually for single use and readout techniques are discrete.

4.3 Integration

In order for wearable sweat sensing to perform optimally in practice, all components need to be integrated into one device or patch. This starts with the integration of the collection and transport means as well as the chemical sensor(s) into a flexible wearable device that can conform with the skin and does not cause major discomfort for the user. Tailored toward the intended use, either a data-processing chip, or a wireless data transmission component, can be integrated into the system to supply a fully automated valuable tool for health monitoring. Although an extensive description of the full integration is outside the scope of this review, a few novel fully integrated features of the wearable part of the device are briefly discussed in this section.

4.3.1 Physical biomarker sensing integrations

In healthcare settings, the information of multiple signals may be necessary to support clinical decisions, for example vital signs such as heart rate, activity level, sweat rate, and oxygen saturation can be combined with chemical biomarker levels measured in sweat to better assess health conditions. Figure 6 shows examples of devices that integrate physical biomarkers sensing with chemical biomarker detection. The device in Figure 6A is a wearable system that consists of a disposable sweat-sensing strip and a smart wristband. Although the sweat collection and sensing of chemical and physical biomarkers is not integrated into one single device, the complete system is fully wearable, transmits data wirelessly to a mobile device, and can measure glucose levels in combination with heart rate, oxygen saturation, and activity levels. By combining sweat glucose concentrations and physiological monitoring data, pre- and postexercise blood glucose levels and blood glucose changes resulting from physical activities are reliably estimated, providing key information for preventing a hypoglycemic shock during intense exercise. Figure 6B shows a stretchable optical sensing patch system that integrates heart rate, oxygen saturation, and sweat pH detection into one wearable device. The system can be used for fitness guidance, skin disease detection, and wound monitoring. The performance of the wearable sensing platform was compared to state-of-the-art measurement equipment, and the results show that the sensor patch system can measure sweat pH with a sensitivity of 4.42 mV/pH from 4.0 to 8.0, heart rate from 25 to 250 bpm, and oxygen saturation from 70% to 100% with an accuracy of ±1 bpm and ±2%, respectively.
The device shown in Figure 6C is a fully integrated device for gout patient monitoring. The wearable sensor is able to measure levels of tyrosine and uric acid combined with monitoring of sweat rate, temperature, respiration rate, and heart rate. The determination of uric acid and tyrosine at a physiological concentration had sensitivities of 3.50 µA/µM/cm² and 0.61 µA/µM/cm², and low detection limits of 0.74 µM and 3.6 µM, respectively. The temperature sensor shows a fast, accurate, and stable response to temperature variations with a sensitivity of −0.06%/°C and a detection limit of 0.051°C. The respiration and heart rate sensors also show a high stability and accuracy when the results are compared with results from the Food and Drugs Administration (FDA) approved measurement devices.

4.3.2 Drug delivery integration

Another interesting integration into a wearable sweat sensor would be a drug delivery system that could be reacting directly to the measured analyte levels by means of administering of medication. Lee et al. have studied this integration by measuring glucose levels in combination with a transdermal drug delivery module, depicted in Figures 7A and B. The measurements of sweat glucose levels are corrected in real-time based on pH, temperature, and humidity. Further studies on the correlation between glucose levels of blood and sweat are however necessary before such wearable devices can be applied in daily use for helping diabetic patients.

4.3.3 Sweat stimulation integration

Dealing with low volumes of sweat is one of the major challenges toward fully functional wearable sweat-sensing devices for sedentary patients who produce very low sweat volumes, in the order of tenths of nanoliters per minute per sweat gland, as described in Section 2.3. Therefore, research is being carried out on the integration of sweat stimulation into the wearable device. Figure 7D shows a device that integrates sweat stimulation by means of chemical stimulants, that is, iontophoretic delivery of the cholinomimetic drug carbachol. Incorporating sweat stimulation mechanisms into wearable devices opens the possibility of monitoring individuals at rest while not having to make adaption to the current devices to reduce the necessary sample volume. However, as explained in Section 2.4 the composition of sweat can change depending on the method of sweat stimulation, and this should
FIGURE 7  Integration of sweat sensing with drug delivery and sweat stimulation. (A)(B)(C) These wearable sweat sensors are developed for sensing of glucose and integrated drug delivery. This system incorporates a heater, sensors for temperature, humidity, glucose, and pH and polymeric microneedles that release drugs upon thermal activation. Reprinted with permission80,124; Copyright 2016, Springer Nature. (D) Integrated sweat stimulation could be a solution for monitoring the health status of sedentary individuals. This device actively increases the sweat rate by iontophoretic delivery of the cholinomimetic drug carbachol. Reprinted with permission 53; Copyright 2017, Royal Society of Chemistry

be taken into account when the measured results are interpreted.

4.4 Commercialization Efforts

A number of established companies and start-ups have commercial interest and own intellectual property in the field of wearable sweat-sensing devices. This section will give a brief description of those companies in an alphabetical order.

Alcopro, a company in the field of drug and alcohol testing, commercializes a sweat patch drug testing system designed for testing of marijuana, cocaine, opiates, (meth)amphetamine, and phencyclidine (PCP) displayed in Figure 8A. The device consists of an absorbing pad for sample collection kept in place by an adhesive film but does not include sensors. After wearing the sweat patch for 7 days, the sample is analyzed in a central laboratory.

BACtrack specializes in breathalyzers, but their product portfolio also includes the BACtrack Skyn Wearable Alcohol Monitor, displayed in Figure 8B, which monitors transdermal alcohol content in real time. However, this product is for research use only, and it is not cleared or approved by the FDA.

Eccrine Systems is founded as a spin-off of the Novel Device Lab headed by Prof. Heikenfeld of the University of Cincinnati. Figure 8C shows one of their devices still in development, mainly focused on monitoring of small molecule drug levels in sweat utilizing local sweat stimulation. Their research work and publications look promising, and they own many patents related to the continuous, on-body measurement of sweat analytes, but none of the device of Eccrine systems have yet been commercialized.

One of the products of the in-vitro diagnostics consortium ELITechGroup is the Macroduct Sweat Collection System, displayed in use in Figure 8D. This system consists of three processes, namely stimulation, collection, and analysis of sweat, and is an established method for diagnosis of cystic fibrosis. The first part, stimulation, is accomplished by pilocarpine iontophoresis. Next, the sweat is collected in a disposable strap-on microfluidic plastic device, shown in the inset of Figure 8D. Finally, the results are analyzed in either a microsample chloridometer or the Wescor Sweat-Chek Analyzer, measuring the total electrolyte content of the sweat specimen.

Epicore Biosystems has developed on-skin wearable microfluidic devices for measuring biomarker concentrations in sweat. The company is a spinout company from Northwestern University Center for Bio-Integrated
Electronics founded by Prof. Rogers. Currently, they partner with Gatorade to develop the Gx Sweat Patch, illustrated in Figure 8E, which provides a system for personalized sports nutrition and recovery recommendations to athletes. The patch can measure the sweat rate and sodium chloride concentration, by means of microfluidic collection and colorimetric sensing. Gatorade states that the Gx Sweat Patch will be available to consumers in the second half of 2020.

Kenzen is developing the Kenzen patch, displayed in Figure 8F, which is used for monitoring of industrial workers and at-risk individuals in health and safety environments. The sweat patch monitors the variables related to heat stress, which are heart rate, sweat rate, body temperature, and activity levels. The patch is currently still in development and is not yet commercially available.

Nix is a consumer diagnostic company that is developing a sweat sensor to monitor hydration levels for athletes, soldiers, and laborers. Currently, the sweat sensor is in research and is not yet commercially available.

Pharmchem, a pharmaceutical ingredients company, also sells the PharmChekQR Sweat Patch, displayed in Figure 8G, for the collection of sweat by absorption for the detection of drugs. After wearing for up to 10 days or longer, the sweat patch needs to be sent to a laboratory for analysis, that is, the patch does not include sensors. This product is commercially available, however cannot be classified as a fully wearable sweat-sensing device because of the need for analysis in a laboratory.

Scram Systems operates in the criminal justice market. One of their products is the SCRAM CAM, a transdermal alcohol testing ankle bracelet for continuous alcohol monitoring, displayed in Figure 8H. The bracelet does not collect sweat, but measures the alcohol concentration in vapor releasing from the skin, which is partially created by evaporating sweat. The bracelet sends the data wirelessly to a base station connected to a digital data monitoring system.

Xsensio is spin-off from the Swiss Federal Institute of Technology, developing an MEMS-based sensing array for the detection of a multitude of biomarkers from sweat. Their research is focused on development of the sensing parts, and integration into a wearable device is not the focus.

As can be concluded no fully wearable sweat-sensing devices are yet commercially available. Only the Macroduct device for the diagnosis of cystic fibrosis from sweat...
CHALLENGES AND PERSPECTIVES IN SWEAT SENSING

Despite its advantages, sweat sensing is not yet an established method for health monitoring of individuals. Design and fabrication of wearable sweat sensors is a growing research topic; however, commercialization of those devices is mainly in its infancy. Furthermore, first efforts into modeling the functioning of the sweat gland have been published and are a good starting point for more elaborated models and validation studies. This section identifies the challenges and important considerations of sweat sensing providing the perspectives toward clinical acceptance of wearable sweat-sensing devices.

Available sweat volumes. For patients in a sedentary state, without elevated sweating as a result of a disease, the sweat rate is in the order of subnanoliters per minute per eccrine gland. Collection and transport of such small sample volumes require sophisticated microfluidics to enable sufficiently fast transport from a collection site to a sensing site. In addition, the physiological mechanisms for temperature regulation cause the fast evaporation of small droplets on the skin. Measures have to be taken into account in the microfluidic design to minimize evaporation, not only to ensure that sweat reaches the sensors but also to prevent accumulation of dried components from sweat hindering reliable and reproducible flow.

The skin surface is a source of contamination. Several sources of contamination can be found on the skin, such as dead skin cells, sebum, analytes diffusing through the stratum corneum, and condensate of transepidermal water loss. This needs to be accounted for in the sweat sensor design and the signal analysis.

pH differences can cause deviations in the measured results. Depending on the utilized sensing technology, sensor readings may be influenced by a changing pH. A pH change can be caused by skin contaminants, disorders, or excreted components. Consequently, sensors should be stable for such deviations, an integrated pH sensor may be considered for correction purposes, this effect must be taken into account in the signal analysis, and/or measures must be taken to standardize the pH of sweat before reaching the sensor.

Some interesting components of sweat, such as cytokines, are only present in trace amounts. These low concentrations require very sensitive and robust sensors. An additional problem is that the detection of these trace amounts in tiny sample volumes can result in skewed or unreliable results because of low sample statistics.

Sweat glands are active in periodic intervals and do not produce sweat constantly. When designing a suitable collection method, this needs to be taken into account. Furthermore, this also affects the temporal resolution that can be reached; for example, typically an eccrine gland is active for about 30 s and nonactive for 150 s, hence sampling within a few minutes might not be possible because no sweat is generated.

The metabolism of the sweat gland can interfere with the measurements. The concentration of sweat metabolites in sweat is influenced by the metabolism of the sweat gland itself, for example, when a sweat gland produces more sweat the lactate concentration in the secreted sweat is higher, and can therefore have another link with the health condition than expected. Other examples of biomarkers that might change due to gland activity include glucose and interleukin-8.

Measurement interpretation. The interpretation of the obtained measurement results is crucial in order to assess the health condition of patients. Either sweat analyte levels need to be correlated to blood analyte levels and linked to health conditions using the state-of-the-art knowledge or novel models need to be designed to be able to link a sweat analyte concentration, possibly in connection with physical biomarkers, to health conditions. A complicating factor is that sweat metabolite concentrations are influenced by the metabolism of the sweat gland itself. For instance, when a sweat gland produces more sweat the lactate concentration in the secreted sweat is higher, possibly leading to misinterpretation of the actual health condition. Solving this may be supported by developing physiological models of the sweat gland that could foster the identification of the complex relationship between blood and sweat content, providing quantitative parameters that cannot be easily obtained noninvasively.

Inter- and intraperson variability. Skin topography, sweat rate per gland and number of active sweat glands, can vary largely between people but also between measurement sites on one individual. There are many known factors that cause inter- and intrasubject variation in sweat production. Main intersubject variability determinants are: physical maturation, hydration, diet, and acclimatization. Main factors for intersubject variability are: the time of day, region of the body being sampled, and the method of sweat induction. The variations caused by these factors complicate parameter estimation and can disturb correlations between biomarkers in sweat and blood composition. Therefore, correlations can possibly be found in the future by employment
of accurate measurement protocols. These protocols may include more frequent measurements at different times to register variations over the day.

Incomplete knowledge about the physiology of perspiration. Despite an overall qualitative understanding on how eccrine sweat glands work, part of the mechanism behind sweat production remains unclear. Examples of this are the mechanisms behind the pulsatile sweat excretion and the role of the sweat glands’ dark cells and myocytes in sweat production. In addition, the pathway from blood to sweat of certain sweat components is unknown, such as drugs, heavy metals, calcium, interleukins, urea, and hormones such cortisol.

Inaccuracies or incomplete quantitative information on perspiration. Quantitative measurements of the amount/concentration, reaction kinetics, and cellular compartment of many cellular components (enzymes, transmembrane proteins) are rare, despite the quantity and quality of experiments increasing rapidly. Furthermore, most available information on sweat composition is based on studies that have collected sweat on an aggregate basis rather than a single gland basis. The data obtained are sometimes conflicting or of questionable quality because of sample contamination. Information on a single gland basis would allow for more insight in per gland variation as well as more insights in the sweat rate. Furthermore, it can clarify to what degree the sweat rate is caused by the expulsion frequency and to what degree it is achieved via the expulsion volume. Differences in sweat composition per gland can further provide interesting information on the physiological process.

6 | CONCLUSIONS

Wearable sweat sensing is gaining interest from both a research and industrial perspective, pushing technology to the market. However, as of today sweat sensing is still far from being an established test method in healthcare setting. While sweat seems an ideal candidate for patient monitoring because of its nonobtrusive accessibility and rich biomarker content, the challenges that come along with sampling, transporting, sensing, and clinically interpreting of components in sweat are still substantial. However, the authors believe that sweat sensing does have the potential to become an established method used in healthcare settings. In vivo experiments, ideally on a single gland basis, can help resolved part of the lack of information to stimulate the development of physiological models providing an accurate description of the eccrine sweat gland, which will lead to a better understanding of partitioning of biomarkers from the blood to the sweat and the link the health/disease conditions. Smart technological solutions in the field of microfluidics and sensing technologies could realize wearable sweat-sensing devices for prolonged, semicontinuous, and nonobtrusive health monitoring.

CONFLICT OF INTERESTS

The authors declare no conflict interest.

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ORCID

Emma J.M. Moonen MSc https://orcid.org/0000-0002-2053-3408
Jaap M.J. den Toonder PhD https://orcid.org/0000-0002-5923-4456

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AUTHOR BIOGRAPHIES

Emma Moonen received her B.Sc. and M. Sc. in 2017 and 2019, respectively, both in Mechanical Engineering from Eindhoven University of Technology. During a research internship at the University of Cambridge she studied making flexible transparent electrodes. Her graduation research was focused on the design, fabrication and testing of point-of-care technology. She is pursuing Ph.D. in the Microsystems group of Prof. Jaap den Toonder, where she focuses on the design of a wearable sweat-sensing device for patient monitoring.

Jaap den Toonder is a full Professor and Chair of the Microsystems section at Eindhoven University of Technology. He received his Master’s degree in 1991 (cum laude), and his Ph.D. (cum laude) in 1996, both in Applied Mathematics from Delft University of Technology. In 1995, he joined Philips Research Laboratories in Eindhoven, The Netherlands, where he worked on a wide variety of applications. In 2008, he became Chief Technologist, leading the R&D programs on (micro-)fluidics and materials science and engineering. Next to his main job at Philips, he was a part-time professor of Microfluidics Technology at Eindhoven University of Technology between 2004 and 2013. Jaap den Toonder’s research focuses on the investigation and development of novel microsystems design approaches and out-of-cleanroom fabrication technologies. The application focus is on microfluidic chips, biomedical microdevices, organs-on-chips, and soft microrobotics. The section’s research approaches are often biologically inspired, translating principles from nature into technological innovations. Jaap den Toonder has (co-)authored over 100 scientific papers, as well as over 40 patents, and he has given more than 50 invited lectures at international conferences. He teaches courses on microfabrication methods, microfluidics, and heat and flow in microsystems, in which hands-on learning is a key element. Jaap den Toonder is recipient of an ERC Advanced Grant in 2019.

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