MEDICINE

Sweat as a diagnostic biofluid

Skin-interfaced microfluidic systems help assess health status and chemical exposure

By **Da Som Yang, Roozbeh Ghaffari, John A. Rogers**

Eccrine sweat glands in the skin are key components of an ingenious system for evaporative cooling. Their action is controlled by the sympathetic nervous system in an adaptive, closed-loop manner to help maintain thermal homeostasis during physical or mental exertion or exposure to high temperatures. Sweat not only removes heat but also helps excrete other chemicals and metabolites from the body. Recent advances in engineering have enabled eccrine sweat to be used for diagnostic purposes, in the form of soft microfluidic analysis systems (*1*, *2*) that gently adhere to the skin for in situ capture, storage, and biochemical evaluation of directly sourced microliter samples. These noninvasive technologies create a broad spectrum of possibilities for using sweat to assess health status and chemical balance, screen for disease conditions, monitor loss of essential chemical species, and detect trace toxins or exogenous agents without the need for external sample collection and analysis.

Eccrine glands appear across all regions of the body; in most circumstances, they are responsible for the largest total volume of sweat loss. The other two main types of sweat glands present in the dermis layer, the apocrine and apoeccrine glands, produce sweat with comparatively complex and variable chemical content. They also do so from specific anatomical regions that are not readily accessible given their location and hair coverage. These considerations motivate the choice of eccrine glands as a central focus for sweat analysis.

The historical standards for sweat assays rely on collection into absorbent pads or tubes followed by analysis with benchtop instrumentation. Quantitative measurements of the dynamics of sweating and the contents of sweat determined in this manner provide important insights into physiological health, psychological stress, nutritional balance, and exposure to foreign substances. Well-established examples include medical testing for cystic fibrosis (CF) based on chloride concentration (*3*), drug screening for banned substances through trace analysis (*4*), and hydration status for sports performance monitoring water and electrolyte loss (*5*).

Unlike blood and interstitial fluid sampling, sweat is collected noninvasively and also avoids issues in contamination, irritation, and inconveniences associated with other noninvasive biofluids such as saliva, tears, and urine. However, requirements for specialized equipment, skilled technicians, and strict protocols have limited the broad utility of sweat for routine diagnostics. Wearable microfluidic patches can perform analysis in real time—in a simple, cost-effective, and noninvasive manner—in nearly any setting, without the need for trained personnel. These devices are usually targeted at a single or specific set of compounds rather than the broad spectrum of sweat constituents. However, in situ analysis of sweat samples could be applied to a broad range of applications with medical relevance, including disease screening for CF, managing kidney disorders, tracking stress levels, monitoring of immune responses, and guiding the use of prescription drugs.

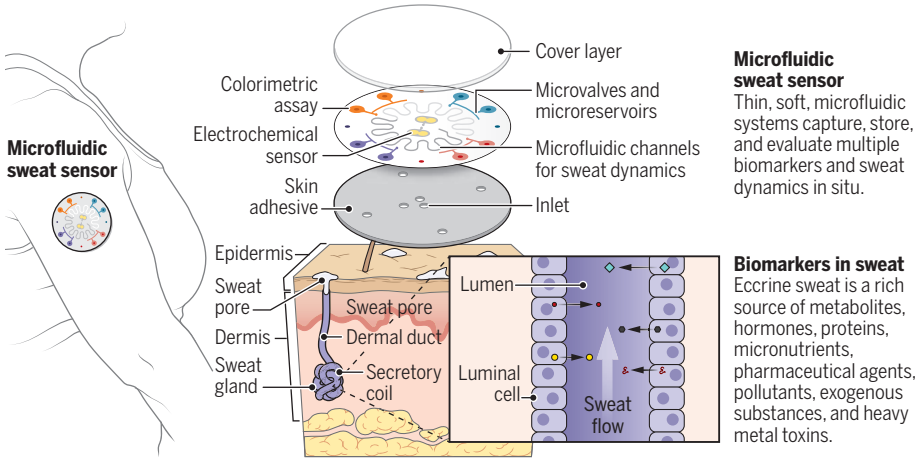
Skin-interfaced microfluidic devices leverage the natural pumping action of the eccrine glands, originating in secretory coils that connect through tubular lumen to ducts through the dermis and the epidermis, terminating at the surface of the skin (see the figure). Stimulation by cholinergic nerve endings that surround these coils drives an influx of Ca^{2+} ions into the surrounding cells and leads to transport of Cl^- and Na^+ ions into the lumen. A corresponding increase in the concentration of NaCl relative to that of the surrounding cells and interstitial spaces creates an osmotic pressure gradient that drives water into the lumen, ultimately manifesting as sweat that exits the skin pores (*2*, *6*).

The rates of flow and the volumes of sweat released from the skin depend on essential aspects of health and hydration status. In addition, active and passive transport mechanisms lead to diverse chemical content, spanning hundreds of constituents, including electrolytes, metabolites, hormones, proteins, pharmaceuticals, nutrients, organic pollutants, and heavy-metal toxins (*5*, *7*). Diagnostic insights based on concentrations of these species benefit from and frequently require precise knowledge of sweat rates; accumulated volumes of sweat loss; and often, body temperature, physical exertion, and cardiopulmonary activity.

Capabilities for these measurements follow from recently developed technologies. Soft, flexible microfluidic systems can establish robust, water-tight adhesive interfaces to the skin (*1*, *2*). These skin patches collect sweat directly as it emerges from the pores in the skin, passing through inlet ports on the base of the device into a network of microchannels and

Analyzing a chemically rich biofluid

Soft, skin-interfaced microfluidic sweat analysis systems enable assessments of health status, chemical balance, and environmental exposure.



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Querrey Simpson Institute for Bioelectronics, Northwestern University, Evanston, IL 60208, USA. Email: ds.yang@northwestern.edu; rooz@northwestern.edu; jrogers@northwestern.edu

microvalves to microreservoirs for storage, sensing, or both. The devices allow measurements of the dynamics of sweat release. Monitoring regional sweat rate and accumulated sweat volume enable tracking of whole-body parameters for estimating loss of electrolytes and other chemical species through sweating. This sensing capability follows from devices that exploit microfluidic systems for capture, storage, and biomarker analysis of sweat. Integrated valves allow sequential routing into corresponding reservoirs, without mixing, as the basis for chronometric separation of consistent volumes of sweat samples over time. These sensors are validated against standard clinic assays for individual biomarkers such as gas chromatography–mass spectrometry or high-performance liquid chromatography. Microfluidic sweat devices used for capturing, manipulating, and analyzing minute volumes of sweat are essential to achieve sweat biomarker standardization and to mitigate the risks of environmental contamination or handling error in remote settings.

Colorimetric and fluorometric indicators and chemical assays can yield quantitative assessments of sweat dynamics, loss, and chemistry (*4*). Chemistries that respond to sweat biomarkers through changes in color or fluorescence intensity allow for quantitative measurements through analysis of digital images collected from transparent regions of the microfluidic structures (*4*). Examples of possible biomarkers include glucose, lactate, creatinine, ammonia, urea, chloride, sodium, zinc, iron, calcium, vitamin C, pH, xanthine, ketone, and alcohol (*4*, *8*).

Electrochemical sensors and associated wireless electronics can support additional options in chemical analysis (*9*). Electrochemical methods exist for glucose, lactate, ammonia, uric acid, potassium, sodium, chloride, calcium, zinc, copper, cadmium, lead, mercury, vitamin C, cortisol, caffeine, pH, levodopa, methylxanthine, tyrosine, dipyridamole, acetaminophen, nicotine, and alcohol (*9*, *10*). Electrochemical analysis allows continuous monitoring and applicability over a wide spectrum of analytes but increases device cost and creates limits on wearability that follow from requirements for power supply and data communication.

In all cases, device operation demands activation of the eccrine glands (*4*) through stimulation of thermoregulatory responses, applied most effectively to healthy adults exposed to warm, humid environments (such as a sauna, bath, or shower) or engaged in exercise. For infants, elderly patients, or other vulnerable populations, emerging alternatives include systems for induction of sweating through iontophoretic transport of pharmacological agents (*3*) through the skin and microfluidic device designs for capture of minute volumes of sweat that continuously emerge from the surface of the skin, known as insensible sweat (*7*, *11*).

Initial versions of these wearable technologies are in widespread commercial use for medical diagnostics and hydration monitoring. A prominent example of the former measures the concentration of chloride in sweat for CF screening, using a kit with regulatory certification for capturing sweat in coiled tubes and then analyzing extracted samples with a benchtop chloridometer. Advanced technologies exploit thin microfluidic "stickers" that support both collection and in situ colorimetric readout based on a chloride-based assay (*12*).

This form of analysis provides real-time, clinical-grade screening for CF without the need for trained personnel or benchtop chemical analyzers, at a price (~$10) that is a fraction of that of existing clinical grade sweat tests (~$250). Microfluidic stickers are simple, low-cost alternatives to clinical standards, with improved reliability and suitability for rapid, at-home tests and broad deployment. Investigational examples of wearable sweat-sensing platforms for medical applications appear in the literature but are not yet approved by the US Food and Drug Administration (FDA). This range of applications includes sensing of sweat urea for gout and kidney disease; monitoring of cortisol for physical and cognitive stress management; tracking of cytokines [such as interleukin-1α (IL-1α), IL-1β, IL-6, IL-8, tumor necrosis factor (TNF), and transforming growth factor–β (TGF-β)] for assessments of immune responses; and guiding the use of drugs relevant to neurological diseases, such as levodopa with Parkinson's patients (*4*, *11*).

A consumer version of this device concept is now available for applications in sports performance to determine whole-body loss of water and electrolytes through sweating. This system pairs with a smartphone application that provides quantitative, personalized feedback to guide rehydration and replenishment (*13*). Recent platforms both extend these capabilities in sweat monitoring and add sensors of complementary biophysical parameters (*14*). One such system monitors signs of heat exhaustion and dehydration for first responders and manual laborers. The technology integrates a single-use, skin-interfaced microfluidic system with a multiuse wireless electronic module for digital sensing, wireless communication, haptic alerts, data storage, and analytics (*4*). Large-scale validation studies with firefighters and workers in the oil and gas industry involve continuous measurements of sweat rate, sweat loss, electrolyte loss, skin temperature, and physical activity.

Other commercial devices integrate electrochemical sensors in wrist-worn bands to measure the concentration of ethanol in sweat, as a surrogate for blood alcohol. Assessments of additional biomarkers in sweat requires advanced analytical techniques to collect sweat samples by using absorbent pads, tubes, or microfluidic systems, each with FDA clearance and registration. Applications include screening for drugs (such as fentanyl, oxycodone, or hydromorphone) and measuring inflammatory cytokines such as IL-6. Ongoing efforts seek to establish lateral flow assays for these and other biomarkers (such as cortisol), with options for integration into microfluidic platforms that also support programmable modules to actively induce sweat for analysis or release components for transdermal delivery of drugs, vitamins, and chemical stimulants (*8*, *14*, *15*).

From the standpoint of human physiology, sweat is well established as a mechanism for loss of essential body substances and as a binary indicator for exposure to exogenous chemical species. By contrast, relationships between certain aspects of sweat chemistry and blood chemistry remain poorly understood. Research that addresses these uncertainties could apply across both known sweat biomarkers and newly discovered ones to further expand options in clinical application. With the addition of advanced electrochemical sensors, sweat collection strategies, closed-loop feedback systems, and transcutaneous drug and supplement delivery modules, future versions of soft microfluidic platforms may enable fully automated modes of operation that combine measurements of medical biomarkers, with clinical reporting and corresponding drug and nutrient delivery. ■

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