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Skin-interfaced colorimetric microfluidic devices for on-demand sweat analysis

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As sweat biomarker levels are continuously changing over metabolism and daily activities, pathological and physiological processes can be dynamically analyzed by wearable devices. The colorimetric skin-interfaced microfluidic devices that do not have external circuit modules exhibit enhanced deformability with a small footprint. However, it is difficult to achieve sampling over time and self-feedback for closed-loop systems. This review summarizes recent advances in microfluidic valves for biofluid management and chrono-sampling, as well as active triggers in microfluidics self-feedback. After enumerating the current limitations in temporal resolution and reliability, we further point out a few potential feasible strategies for future developments.

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INTRODUCTION

The increasing demand for preventive health/fitness monitoring has led to rapid developments of wearable devices that can detect biophysical and biochemical signals over various activities[1–12]. Different from invasive/inconvenient blood sampling and intermittent sampling from urine, saliva[13], tear[14], or interstitial fluid[15,16], continuous in situ sweat analysis can be performed on most of the body surface due to sweat generation by human thermoregulation[9,17] or local chemical stimulation[18]. Meanwhile, a large number of biomarkers in sweat have been correlated with the concentrations of circulating analyte in blood. Continuously monitoring changes in the concentration of these sweat biomarkers provides opportunities for early diagnosis of many diseases[19], including cystic fibrosis, diabetes, and gout based on monitoring of chloride[20,21], glucose[22,23], uric acid and tyrosine[24]. In addition, tracking sweat loss would provide personalized and time-sensitive feedback to athletes, military personnel, and physicians in clinical care for in-time water intake, which can prevent dehydration or heat stroke[25–27].

It is vital to collect, capture, and subsequently analyze (discrete) sweat samples at well-defined time points across body positions, leading to the efforts in the development of both electrochemical and colorimetric sweat sensors[5,28]. With the bio-sensitive substances (e.g., enzymes, non-enzymatic nanomaterials, aptamers, molecularly imprinted polymers) decorated on the working electrode, the electrochemical biosensor can capture the target analyte and generate an electrical signal that correlates with the concentration. The sensor can either analyze the sweat with onboard electronics on skin[29] or collect sweat with a microfluidic network for subsequent analysis[30,31]. With the circuit module[32], the detection results can be transmitted to and displayed on terminal devices such as computers and mobile phones for visualization[33]. Both enzymatic and nonenzymatic electrochemical biosensors are widely explored[34], with the former involving the use of enzymes and the latter using non-enzymatic nanomaterials. The enzymatic sensors often showcase high selectivity (e.g., enzymatic glucose sensor using glucose oxidase[29,35]), but they are expensive, less stable over time, and are affected by environmental conditions[36–38]. In contrast, nonenzymatic sensors can exhibit high sensitivity, relatively good selectivity, and high stability[30,39]. But they often show slow reaction kinetics, poor selectivity compared to enzymatic sensors, and the need for alkaline solutions[40,41]. Efforts to address these challenges have led to the exploitation of (1) nanostructured electrodes for increased contact area with the bioanalytes, and (2) a porous cavity containing mild alkali solutions for sweat glucose analysis[30]. Nevertheless, these electrochemical sweat devices in various forms (e.g., wristband More accurate results in[29], headband[42], or skin patch[18]) provide real-time and convenient readout[32,43–45]. However, electronic modules inevitably increase the cost and footprint of the resulting wearable devices and have compliance issues for the elderly[46].

Different from electrochemical sensors, colorimetric sweat sensors are more compliant, low-cost, and easy to use due to the elimination of electronics (used for data analysis and transmission). Used as color indicators, the chromophore molecules can change their electron state when interacting with target biomarkers to result in the absorption of photons with different wavelengths, visualized as color changes with intensity correlated with the concentration[28]. The colorimetric assays with dry reagents added to the reaction chamber can detect a series of biomarkers, including metabolites, electrolytes, and micronutrients. For instance, the generated H_2O_2 form glucose oxidation changes colorless o-dianisidine into red-colored oxidized o-dianisidine, which can detect glucose in range from 0.1 to 0.5 mM with a limit of detection (LoD) of 0.03 mM[47]. Similarly, the increase in the lactate concentration from 0 to 30 mM oxidizes 4-aminoantipyrine to change the color from yellow to purple with LoD of 1.58 mM[48]. The chloride ions (Cl^-) reacts with silver chloranilate to produce a color response from white to purple in proportional to Cl^- concentrate from 0 to 120 mM with LoD of 10 mM[21], whereas calcium ions (Ca^{2+}, 0–15 mM) reacts with o-cresolphthalein complexone (o-CPC) to yield a violet-colored complex (LoD of 2 mM)[49]. The detection of vitamin C relies on the reduction of ferric ion (Fe^{3+}) to ferrous ion (Fe^{2+} during interaction with vitamin C in the range from 0 to 100 μM to generate a compound with a color change to pink (LoD of 2 μM)[50]. Compared with point-of-care sweat analysis, the wearable colorimetric sensors can provide continuous sweat collection

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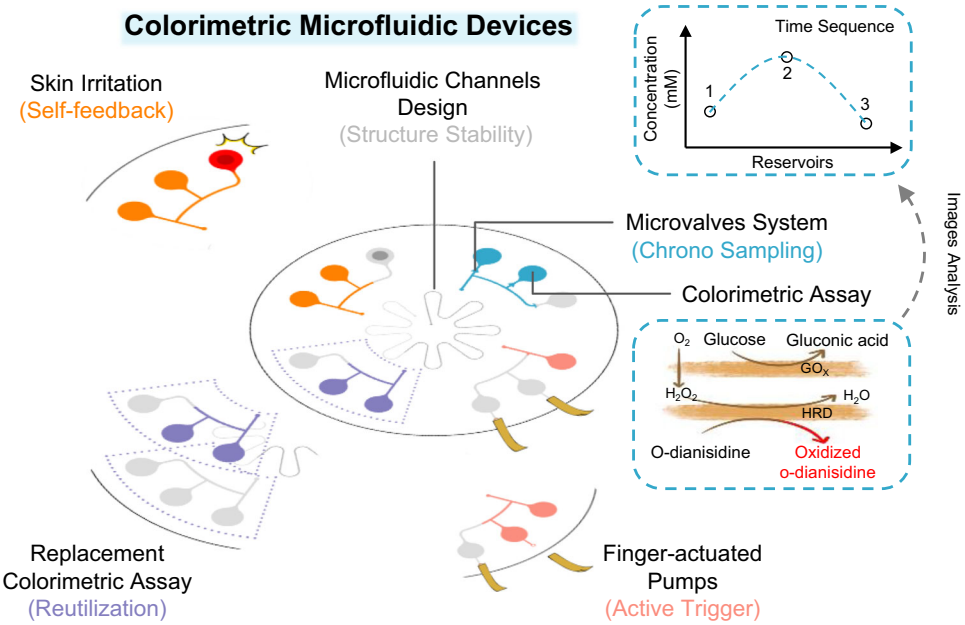

Fig. 1 Schematic diagram of skin-interfaced colorimetric microfluidic devices with colorimetric assay and microfluidic network for sweat analysis and advanced sweat control and feedback.

and analysis over time for early disease diagnostics (e.g., elevated sweat chloride for cystic fibrosis[21] and increased cortisol levels over prolonged time periods for obesity, depression, hypertension, and diabetes[51]). Traditional colorimetric detection relies on the use of a smartphone or the standard colorimetric card for direct comparison because of the difficulty to recognize a single color change with the naked eye[52]. More accurate results in terms of the exact degree of color reaction can be based on a preset coordinate axis in the distance method[53,54] or multicolor colorimetric methods[55]. However, the most used method is relying on the real-time image analysis of smartphones to provide quantitative readout[56,57] require the image to be well-framed and uniformly lit[20,58]. For colorimetric assay measurement, the LAB color space algorithm can be used to accurately extract small differences in color[59], which enhances reliability in practical scenarios with uncontrolled lighting compared to assessments in the RGB color space[60]. Both traditional computer vision and advanced machine-learning algorithms can also be exploited to assist image capture and feature quantification[25,58,61,62]. The irreversible color change of the colorimetric sensor is often associated with (1) single or limited-time use, (2) sweat mixing at different time points, and (3) undesired sweat contamination and evaporation to affect sweat analysis[63]. To address these challenges, the colorimetric sensor is often integrated with microfluidic devices, which also allows the detection of multiple analytes in a single platform[20]. The microchannel connected with a series of independent storage chambers allows sweat sampling and analysis over time, while minimizing the issues from sweat cross-contamination or evaporation. Although the chromogenic reagent is not reversible to provide "continuous" monitoring[64,65], microfluidic networks can be used to separate newly secreted from previous sweat into a series of chambers for temporary storage or sequential detection[66,67] even in intensive contact sports[25] and aquatic settings[27]. Therefore, the rational design of microfluidic devices makes it possible to reliably monitor the concentration variation of biomarkers in sweat with the colorimetric method.

This review briefly outlines the recent developments of colorimetric microfluidic sweat devices, with an emphasis on chronometric sampling and electronics-free control or feedback technologies (Fig. 1). The former mainly focuses on the structural design of microfluidic valves, whereas the latter highlights self-feedback reminders and active triggers for closed-loop sweat analysis systems. After reviewing the current limitations, possible directions for future developments are discussed.

Chrono sampling behavior in colorimetric microfluidic sweat devices

In the electrochemical sweat sensors, the circuit module is often used to first electronically program a microfluidic valving system for active biofluid management[32] and then generate electrical signals based on the collected biofluids for wireless transmission and visual readouts on a smartphone or electrochromic display[18,43].

Without electronic components, the colorimetric sweat sensor can only rely on the natural sweat pressure from osmosis effects to drive sweat through soft microfluidic structures for sweat sampling. Therefore, it is vital to design valve structures in microfluidics to actively manage biofluid flow in microfluidic networks for chrono-sampling and analysis. The commonly used designs include capillary bursting valves[66–70], hydrophobic valves[71], and polymer valves[72].

In the capillary bursting valve (Fig. 2a), the bursting pressure is determined by the microchannel geometry and surface wettability to control the flow of the fluid into different collection chambers[69] in the programmed order[67] (Fig. 2b) for offline analysis[60]. For instance, reducing the dimension of a rectangular channel can increase the bursting pressure according to the Young-Laplace equation[66]. Secondly, the bursting valve enables the individual analysis of multiple biomarkers to be performed in the same microfluidic chip[73]. A series of bursting valves with different burst pressures can also be used to accurately and routinely measure the secretory fluidic pressures generated by eccrine sweat glands at different parts of the body[66]. While the discontinuous flow of sweat may generate bubbles, the bursting valve in each branch of the connected micro-flow channel network can adjust the air pressure in the channel and release the produced bubbles[69]. By modulating the geometry of the microchannel with photolithography, the Tesla valve (Fig. 2c) also accelerates the flow in the forward direction and inhibits the flow in the reverse direction[74,75], resulting in one-direction flow (with high diodicity) for fluid

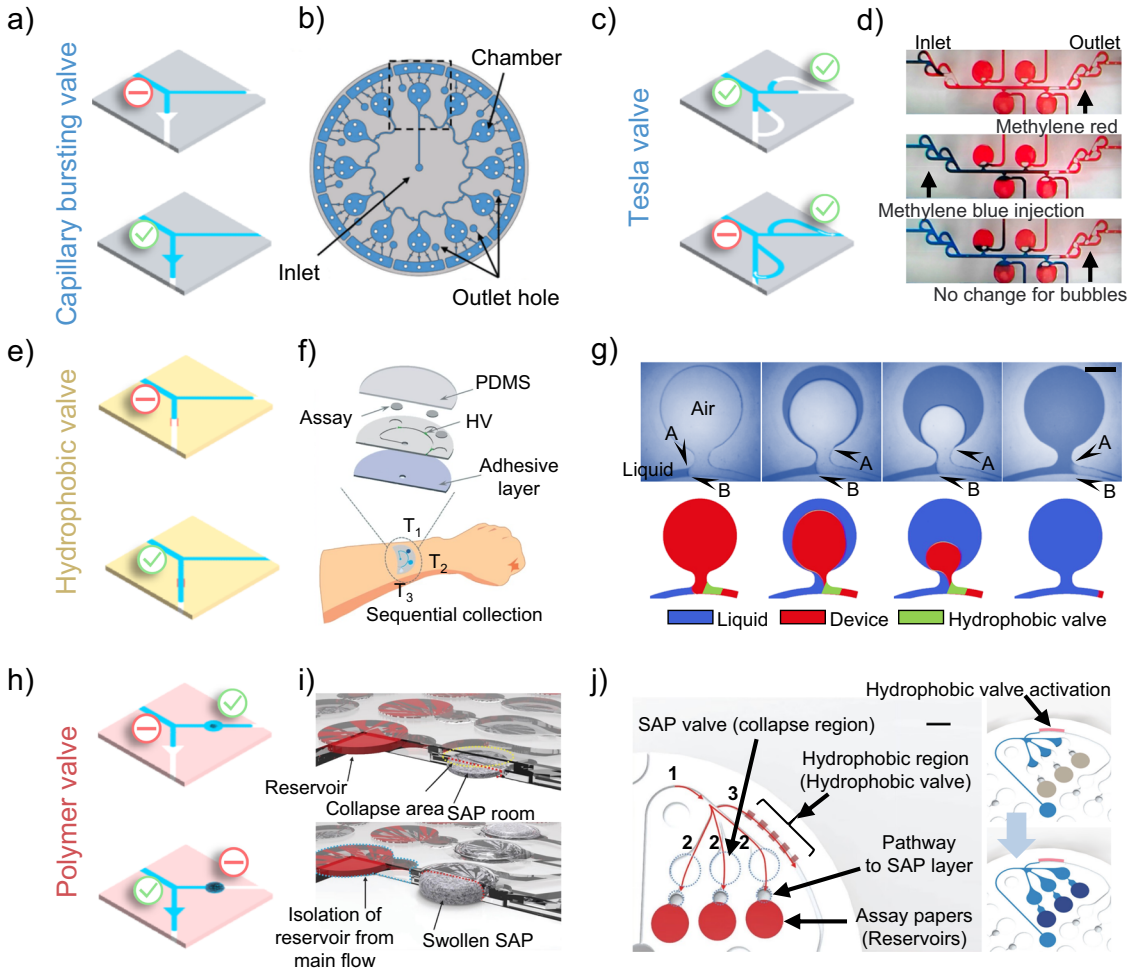

Fig. 2 Skin-interfaced microfluidic chronometric sampling by passive valve structures. a Schematic illustration of the capillary bursting valve. **b** Top view of microfluidic channels for chrono-sampling of sweat[67]. **c** Schematic illustration of the Tesla valve and (**d**) its demonstration in the sampling process using methyl red and methylene blue[74] (increased pressure inside the upper right return channel due to the air pressure). **e** Schematic illustration of the hydrophobic valve (HV) and (**f**) its use in an epidermal microfluidic device with one-opening chambers, along with (**g**) optical images and numerical simulations of the hydrodynamic flow process into the one-opening chamber with a HV[71] (scale bar: 1 mm). **h** Schematic illustration of the polymer valve and (**i**) its use in the super absorbent polymer (SAP) system with valve activation before (top) and after (after) sweat collection[72]. **j** Microfluidic channel design of the combined use of HV and SAP valves with reservoirs[72] (scale bar: 0.5 mm).

controls. The driving force for the flow in the Tesla valve from the pressure difference between the inlet and outlet[56] allows the fluid to flow from the high-pressure to low-pressure area (Fig. 2d)[74]. The resulting sweat collection chip prevents backflow at the entrance and restrains the flow to contact the outside at the exit. Without any mechanical structures, the Tesla valve optimizes stability and provides a reusable wearable microfluidic device.

Different from the capillary bursting (Tesla) valve that explores geometric changes of the microchannel, the hydrophobic valve relies on the modulation of the wettability in the inner surface of the microchannel (Fig. 2e). The hydrophobic valve is often prepared by exposing the other (except for valve) regions with plasma to generate hydrophilicity[72]. However, hydrophobic recovery occurs within hours in the ambient environment[76]. Efforts to address this challenge include subsequent surface modification of the plasma-treated PDMS with low-energy polyvinylpyrrolidone (PVP), resulting in long-term stability (6 months)[77]. Introduced at the junction of the chamber and the microfluidic channel, hydrophobic valves can result in the design of one-opening chambers to significantly reduce evaporation and contamination of sweat samples during collection and storage for enhanced accuracy (Fig. 2f)[71]. The hydrophobic valve blocks the advancing front of the liquid so it can spontaneously wick into the hydrophilic chambers, followed by bursting the hydrophobic valve to continue onto the next chamber for sequential collection and chrono-sampling (Fig. 2g). The same mechanism could also be applied to paper-based wearables[78,79] by embedding the hydrophobic channel barrier (e.g., with wax printing[62,80]) in the hydrophilic paper microfluidics to direct sweat flow. Because of the capillary flow into the porous paper that causes saturation[81] and its disposable nature, most paper-based microfluidic devices are designed for one-time use only. Combined with a sweat evaporator and pre-defined hydrophobic barriers to drive the continuous sweat flow, the paper-microfluidic devices can allow the flow of fresh sweat across the electrodes and avoid sweat accumulation[82,83]. However, the durability of paper-based microfluidic devices over long-term use still needs to be thoroughly investigated.

Polymer valves are also simple in design with polymer locally embedded in the microchannel to either expand/contract[32,72] or dissolve[84] for reversible or irreversible control of the fluid flow (Fig. 2h). For instance, the polymer valve triggered by a certain amount of collected sweat swells upon hydration to close the inlet passage and prevent backflow while allowing air ventilation

Table 1. Comparison of different microfluidic valves.

Valve	Capillary bursting valve	Tesla valve	Hydrophobic valve	Polymer valve
Mechanism	Bursting pressure	Diodicity	Surface wettability	Wettable materials
Elements	Microchannel geometry and surface wettability	Difference in flow distribution	Blocking the advancing front of the liquid	Expansion/contraction/ dissolution of polymer
Types of wearables	Polymer	Polymer	Polymer/ paper/fabric	Polymer/paper
Limitations	High precision requirement, long preparation time		Instability of surface modification	Hysteresis, possible sample contamination

(Fig. 2i)[72]. The dissolvable polymer valve mainly used in paper-based microfluidics, on the other hand, gradually dissolves itself upon sweat collection to open the valve made entirely of filter paper after a certain time[84]. The other dissolvable barriers made of sucrose[85,86], trehalose[87], or salts[88] can only slow down the flow (e.g., a delay time of 48 s for the sucrose barrier[86]) without blocking the microfluidic channels, which are suitable for mixing of reagents. The dissolvable polymer valves consisting of dried polymers as a closing valve allow the liquid to flow in sequence to different multisensory transducers for revealing fluctuations in the analyte concentration.

Each type of these valves is associated with advantages and limitations (Table 1) to provide unique application opportunities in chronometric sampling and colorimetric readout. It is also possible to combine different types of valves to leverage the synergy for noninvasive and in situ monitoring of sweat. For instance, the passive polymer valves that route the sweat into the desired reservoirs for analysis and block the channel for preventing backflow after triggering still need to be coupled with other valves (capillary bursting valves or hydrophobic valves) for chrono-sampling. The hydrophobic valves on the primary branches of the microfluidics control the sweat to sequentially close the polymer valves on the secondary branches for stable collection and quantitative analysis (Fig. 2j)[72].

Electronics-free sweat control or feedback technologies

The major challenges of colorimetric microfluidic devices include (1) uncontrolled flow and mixture of sweat, (2) backflow of soluble chemical regents from the reaction chamber to the skin, (3) uncertainty in the precise analysis time due to varied sweat rate, (4) difficulty to perform multi-step colorimetric assays, (5) irreversible colorimetric reaction for continuous analysis, and (6) lack of in-time self-feedback. A potential solution to some of the above challenges could explore the combination of the sweat analysis system with an electronically programmable microfluidic valve that uses the individually addressable microheater to control the sweat flow in the microchannels blocked by the thermos-responsive hydrogel[32]. The active control of the valves allows sweat analysis at user-defined times, independent of sweat flow rate and external disturbances. The electrochemical sweat analysis combined with a wireless flexible printed circuit board (FPCB) also allows reversible sweat analysis and instant feedback. Although a complete solution for electronics-free colorimetric microfluidic devices is yet to be reported, the inspiration from the above electrochemical sweat analysis system and many others could open up opportunities for future developments.

The use of relatively high modulus polymers (e.g., polyurethane resin with a Young's modulus of 1.1 GPa) as relatively rigid but deformable serpentine "skeletal" structures (Fig. 3a)[89,90] in microfluidics devices can minimize errors caused by microchannel deformation or microcavity collapse[91]. The "skeletal" structures are further surrounded by a low-modulus polymer ($E_{substrate,1} = 60$ kPa, $E_{substrate,2} = 1$ MPa) to provide an elastic restoring force and a soft interface to the skin. To prevent the backflow of chemical reagent (and sweat) for reduced risks of potential chemical harm to the skin, the check valve located between the reaction chamber and microchannels can be explored to direct the sweat flow along the pre-defined direction (Fig. 3b)[47].

To perform sample analysis at the user-defined time, the finger-actuated pumps are introduced at the end of microchannels (Fig. 3c)[92]. After collecting the pre-defined amount of sweat in the inlet chamber with excess sweat expelled through the outlet, pulling a thin tab can deform the cavity to generate air pressure to suck the collected sweat from the inlet chamber into the sensing chamber for quantitative analysis on-demand. Besides the analysis on-demand, active triggers in microfluidic wearables can also help reset the device that will saturate with sweat over time. The reset feature can also initiate the collection of freshly secreted sweat to avoid mixing with the previously collected sweat for improved accuracy in biomarker analysis. Upon pulling the bottom of the resettable skin-interfaced microfluidic device, sweat from the collection channel would be sucked into the elastomeric suction pump, and then ejected through the outlet once the strain is released (Fig. 3d)[93]. Acting as a pressure pump, the manually activated reset button can also reset the channel using a negative or positive pressure mechanism (Fig. 3e)[94]. With the reset, expelling the collected sweat from the device once full can provide continuous, prolonged sweat analysis.

The irreversible property of the activated colorimetric assays often renders the colorimetric microfluidic devices to be single-use and disposable. One possible solution to this problem is to replenish the colorimetric assay in a "sweatainer" that is further integrated with an epidermal port interface to provide a long-term and fluid-tight interface with the epidermis (Fig. 3f)[95]. The specific aligned access point on the backside of the epidermal port interface facilitates a rapid replacement of sweatainer within 30 s for a minimized interruption during sweat collection.

The colorimetric microfluidic devices with self-feedback functions to deliver time-sensitive sensations to the skin without electronics can provide critical information such as the physiological status or the device's working status to the users. Therefore, the resulting system can avoid frequent observations and reduce device complexity without using electronics. As a representative example, the sense of touch can provide chemesthesis self-feedback based on an efflux pump that is preloaded with food-grade chemicals (e.g., menthol or capsaicin)[93]. As the amount of sweat reaches a preset threshold for sweat loss, the released menthol or capsaicin causes skin irritation to actively remind the user of water intake (Fig. 3g). Due to the high sensitivity of human skin to temperature[96], the thermal warning from endothermic/ exothermic chemical reactions triggered by sweat such as the reaction between CaO and water is also promising. However, chemesthesis can contaminate the skin and be erratic (depending on different parts of the body and the sensitivity of different individuals[93]), whereas thermal warning requires careful control of temperature and duration to prevent burns[97].

Conclusions and perspectives

Different from the electrochemical sweat sensors, the detection of biomarkers in sweat with colorimetric sweat sensors relies

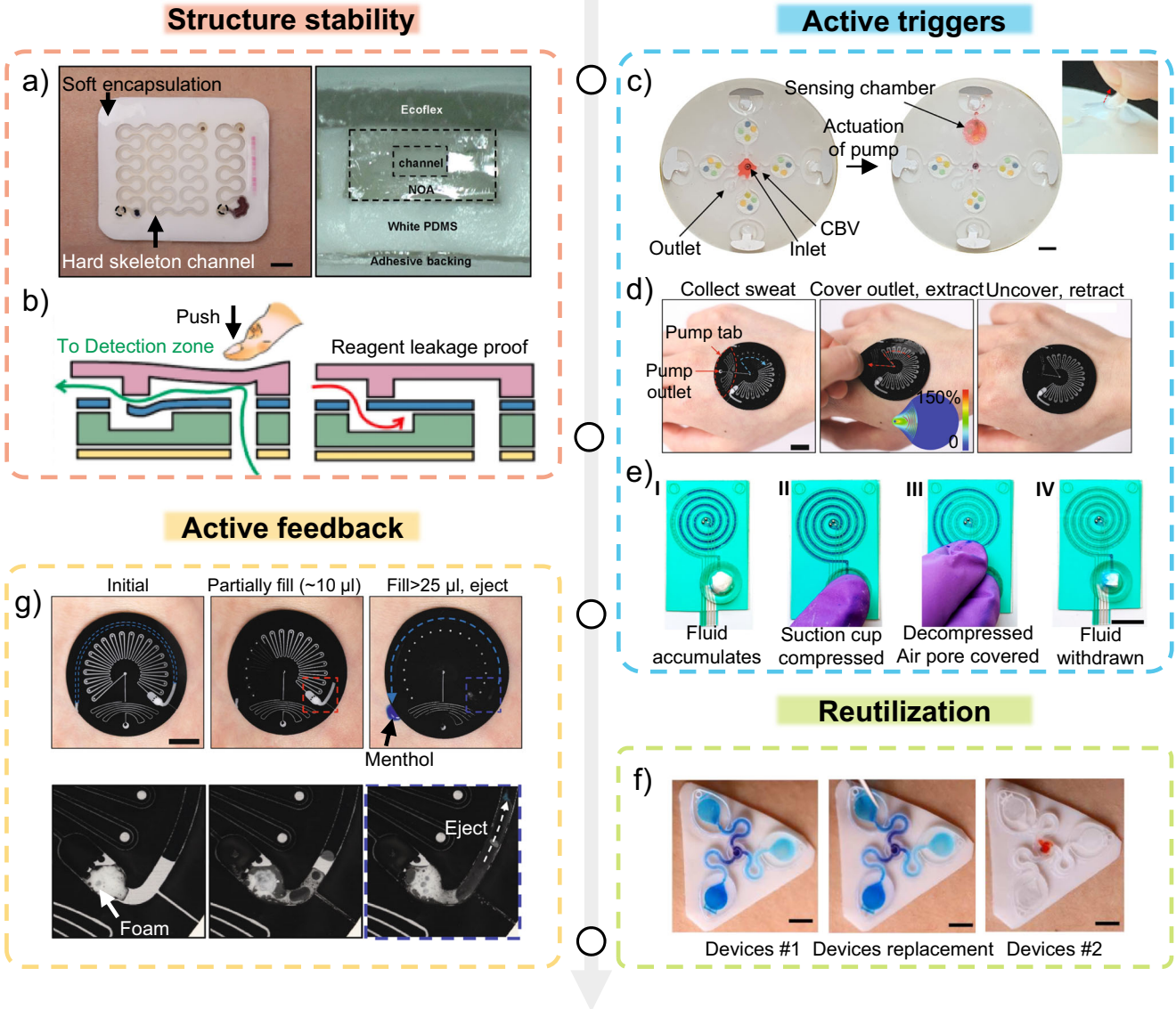

Fig. 3 Electronics-free sweat control and feedback technologies in colorimetric microfluidic devices. Enhanced structure stability with (**a**) rigid microchannels embedded in a soft elastomer[89] (scale bar: 5 mm) and (**b**) check valves in microchannels to prevent reagent backflow[47]. Active trigger with (**c**) finger-actuated pumps for on-demand sweat analysis[92] (scale bar: 5 mm), (**d**) strain-actuated pinch valve for microchannels reset[93], and (**e**) manually activated button for negative pressure suction reset[94] (scale bar: 1 cm). **f** Reuse with replenishment of sweatainer for multiple colorimetric analysis[95]. **g** Sweat-triggered chemesthetic feedback (C.A. = chemesthetic agent)[93].

on the design of valve structures and colorimetric reagents. The design of varying valves with different structures and materials provides opportunities to control sweat flow, chronological collection, and quantitative detection. Combined with advanced sweat control and feedback technologies, the electronic-free colorimetric microfluidic device starts to show the potential for closed-loop devices. Combining colorimetric reagents with different materials such as fabric[42], paper[22,98], and hydrogel[99,100] facilitates the colorimetric readout (e.g., accurate measurements of sweat rate due to measurable swelling and color change in hydrogels[100]). Effectively fixing colorimetric reagents in these well-designed substrate materials also prevents color leaching, chemical diffusion, and spatially nonuniform color responses (caused by the continuous flow of sweat). Despite the significant advances, there are still many grant challenges in the field of colorimetric sweat sensors before they can achieve an improved level of comfort, stable functions upon mechanical deformation, and reliable manufacturing at a low cost for various applications.

The soft and deformable design of the wearables is needed to reduce discomfort and iatrogenic injury, especially for those with delicate skin such as infants[101,102]. However, the deformation of the device during operation or other non-specific external factors can affect the sweat flow behavior in microfluidic devices or even accidentally trigger the feedback component. Although the microfluidic devices with relatively rigid microchannels and soft substrate can be explored to alleviate this issue, the fabrication involves expensive and time-consuming processes (photolithography and deep reactive ion etching with encapsulation over 16 h), as well as large material and modulus mismatch[89,90]. In comparison, the digital light processing (DLP) technology could provide rapid fabrication (<1 h) of 3D printed channels with micron-scale feature sizes (<100 μm) and enhanced optical transparency (Fig. 4a)[95]. Meanwhile, the grayscale in DLP allows

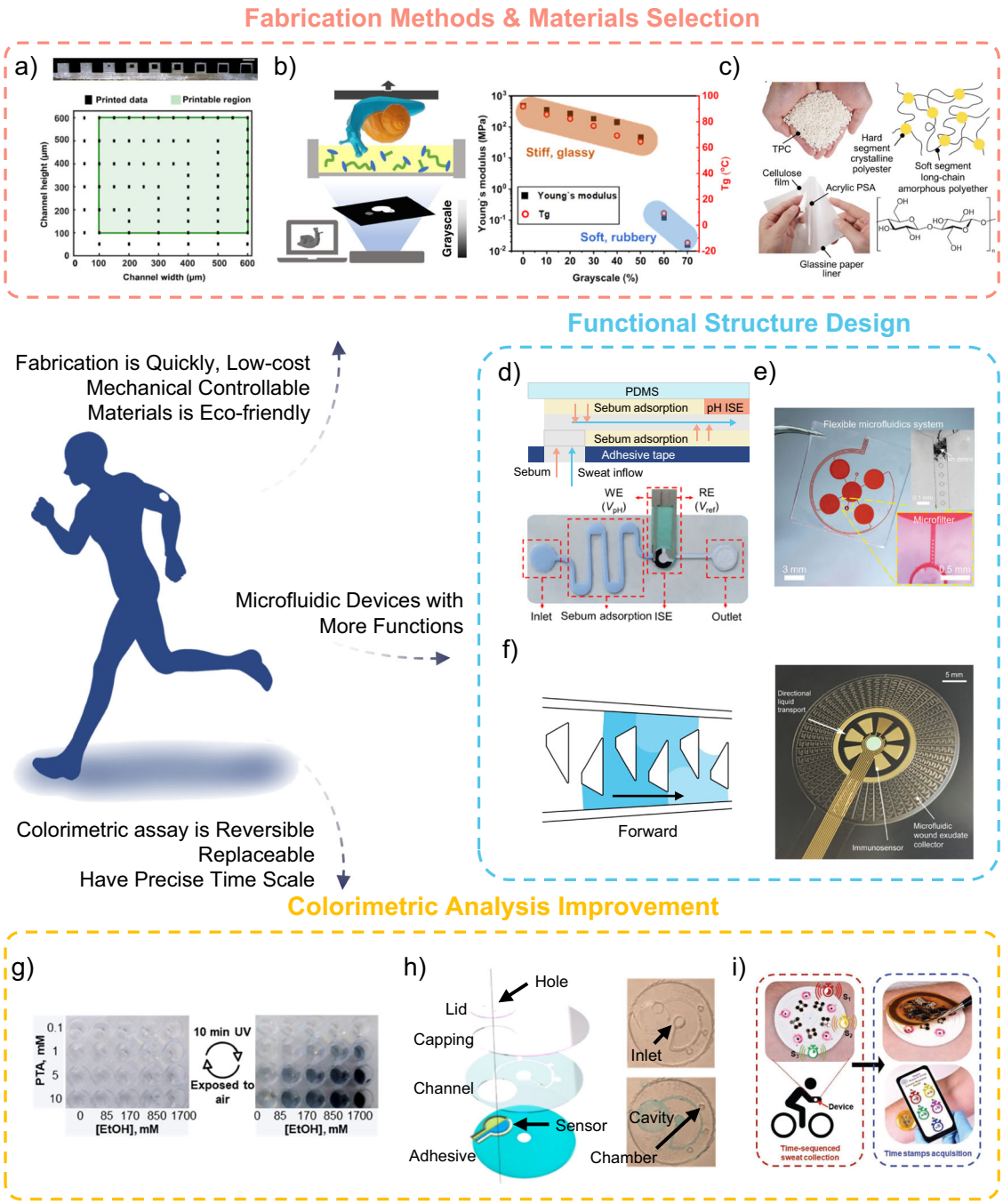

Fig. 4 Future opportunities for wearable colorimetric sweat monitoring systems. The use of digital light processing (**a**) to fabricate microfluidic devices[95] and (**b**) its grayscale to fabricate mechanically gradient materials[103]. **c** Eco-friendly microfluidic devices consisting of biodegradable thermoplastic copolyester elastomer (TPC) for the microfluidic layer and a cellulose film with an acrylic pressure-sensitive adhesive (PSA) for the sealing layer[60]. **d** Common oil-control sheets to filter sebum in sweat[105]. **e** Microfluidic devices with ten micropillars in the inlet to filter microspheres and skin debris[44]. **f** The directional liquid transport system that exploits the interconnected sawtooth-shaped capillary channels with wedge-shaped micropillar array[106]. **g** Color change diagram of PTA/ethanol photo-redox cycle[108]. **h** The exploded view of the integrated microfluidic non-enzymatic glucose sensor with a replaceable porous encapsulating reaction cavity[30]. **i** The colorimetric analysis with precise time point to determine the temporal variations of biomarkers in sweat[109].

the use of different intensities of light to fabricate the functionally graded materials with a mechanical gradient up to three orders of magnitude, mitigating the issue of abrupt modulus difference (Fig. 4b)[103]. To mitigate the environmental concerns from disposed devices, the commonly used silicone elastomer such as PDMS and Ecoflex[104] can be replaced by biodegradable materials. For instance, a biodegradable microfluidic device consisting of thermoplastic copolyester elastomers (TPCs) for the microfluidic layer, a cellulose film and pressure-sensitive adhesive as a sealing layer, and natural chemical reagents as colorimetric assays can be fully degraded in the soil to organic compounds for plant growth (Fig. 4c)[60].

In addition, accurate sweat analysis with skin-interfaced wearables needs to mitigate the contaminants secreted from the skin (e.g., sebum, skin debris, dust). A paper-based sandwich-structured pH sensor that uses common oil-control sheets can

filter the sebum mixed in sweat (Fig. 4d)[105]. With ten micropillars in the inlet for sweat filtration, the integrated microfluidic chip can effectively filter out microspheres with a diameter of 20 μm and skin debris (Fig. 4e)[44]. The micropillars can also be designed into a wedge shape to form a polar array of interconnected sawtooth-shaped capillary channels and allows the continuous flow in the forward (or reverse) direction is facilitated (or inhibited) (Fig. 4f)[106]. Moreover, anti-collapse needs to be considered when designing the micropillars to effectively avoid the collapse of arbitrary-shaped soft microchannels or reservoirs[107].

Most of the colorimetric sweat sensors also suffer from a one-time use of the reagents and non-continuous measurements, despite the recent developments in recyclable colorimetric reagents such as phosphotungstic acid (PTA) for alcohol detection in saliva and sweat. As a colorless photochromic heteropoly acid, PTA can be reduced by ethanol to produce an intense blue color under ultraviolet radiation, which can be oxidized and returned to a colorless state after exposure to air (Fig. 4g)[108]. Before the advent of reversible colorimetric reagents, the use of replaceable colorimetric devices can be an alternative. The design concept of a replaceable porous encapsulating reaction cavity (Fig. 4h)[30] may be leveraged for the robust reagent chamber. It is also of high interest to determine the chamber filling time for obtaining the temporal variation of sweat biomarkers. The colorimetric microfluidic device integrated with sweat-triggered flexible galvanic cells can serve as sweat-activated "stopwatches" to record temporal information associated with the collection of discrete microliter volumes of sweat (Fig. 4i)[109]. The galvanic cells triggered by sweat generate a time-dependent decayed voltage that is recorded and obtained with a battery-free NFC module to serve as a "stopwatch". Although the finger-actuated pumps can provide on-demand sweat analysis, the needed user engagement can be challenging in practical use, so automatic trigger or self-feedback is desirable.

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AUTHOR CONTRIBUTIONS

W.Y.L., H.Y.C. and X.F.W. conceptualized the work. W.Y.L. wrote the original draft; H.Y.C. and X.F.W. reviewed and edited the manuscript. H.Y.C. and X.F.W. provided overall supervision of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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