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Review article

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Wearable flexible microfluidic sensing technologies

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Abstract

Wearable biosensing technologies can provide real-time monitoring of health and disease at the point of care. By integrating flexible microfluidics with wearable biosensors, body fluids can be non-invasively sampled and analysed for reliable, clinically informative, cost-effective and continuous biomedical monitoring. In this Review, we discuss flexible wearable microfluidic sensors for health monitoring and disease diagnosis, highlighting materials and engineering considerations with regard to biofluid collection, analyte calibration, signal interferences reduction, target recognition, and sensor reusability. We outline how such flexible microfluidic-based biosensors can be designed for the analysis of sweat, saliva, tears, interstitial fluid and wound exudate, and examine their applications at the point of care. Finally, we highlight the challenges that remain to be addressed for the clinical translation of wearable flexible microfluidic sensors and discuss future possibilities, including the integration of machine learning and the Internet-of-things.

Sections

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Key points

- Flexible microfluidics can be integrated into wearable flexible sensors to facilitate biofluid sampling and sensing.
- Flexible microfluidic sensors for sweat, interstitial fluid, tears, saliva and wound exudate may advance personalized health care, in particular for metabolic, eye, oral cavity, gastrointestinal and infectious disease management.
- Continuous monitoring by flexible microfluidic sensors can be achieved by exploiting direct or enzyme-based redox reactions or bioaffinity and by applying sensor-regeneration strategies such as programmed electrical stimuli.
- Artificial intelligence can be integrated into flexible microfluidic sensors to design smart point-of-care systems that can aid in medical decision-making by leveraging the Internet-of-things in medicine.

Introduction

The integration of microfluidics with flexible electronics enables the design of flexible microfluidic sensors for disease diagnosis, health-care management and medical therapy[1–5]. Microfluidics are commonly used for filtering and separating particles, sorting and counting cells, drug testing and screening, cell culture, and point-of-care diagnosis[6]. In particular, flexible microfluidics can be seamlessly interfaced with the human body to retrieve and manipulate small volumes of samples (microlitres to nanolitres) for sensing and multiparametric analysis. Integrated with wearable flexible electronics[7–15], such microfluidic platforms can be miniaturized and equipped with sensing, communication, and analysis modules and worn by people with minimum disruption to their daily activities[3–5,16,17]. Thus, integrating wearable flexible electronics and microfluidics allows long-term, user-friendly health-care and disease management, enabling on-site and continuous sampling, sensing and analysis of biomarkers or drugs with minimal body fluid volumes (for example, sweat, saliva and tears), and simple operation[18–21]; for example, small wearable flexible microfluidic sweat patches can continually assess sweat rate[18], nutrient[20] concentrations, glucose[19] and cortisol[21] levels without interfering with daily activities.

With the development of flexible microfluidic[22] and wearable flexible sensors[7–15], various fibrous[23–25] and polymer-based[26] flexible wearable microfluidic sensors have been developed (Fig. 1a). Early flexible wearable microfluidic sensors primarily consisted of simple colourimetric or electrochemical fibrous sensors for pH, sweat rate, and sodium ion detection[23–25] or electrochemical polymeric sensors with wireless communication microelectronics for the analysis of basic analytes such as sweat electrolytes[26]. Subsequently, more complex systems have been developed, including multiplexed or highly integrated wireless wearable flexible microfluidic sensing systems[19–21,27]; for example, a wearable colourimetric patch has been developed for systematic glucose, lactate, pH and Cl^- monitoring[27]. Furthermore, major advances have been made in monitoring more challenging analytes, including various metabolites and nutrients[20] as well as low concentrations of micromolecules such as hormones[28] and inflammatory markers[29].

In this Review, we discuss materials and engineering strategies involved in developing wearable flexible microfluidic-based sensing devices for biomedical diagnosis and monitoring. We provide an overview of fluidic handling strategies, functions, and sensing mechanisms and discuss the materials and design considerations for flexible microfluidic-based sensors. We then present strategies to overcome the limitations of flexible microfluidic-based sensors and highlight challenges that remain to be addressed for their commercialization and clinical translation (Table 1).

Materials and engineering considerations

Wearable flexible microfluidic sensing systems mainly consist of three components: a flexible microfluidic platform, sensors and microelectronics (Fig. 1b,c and Box 1). The flexible microfluidic platform includes inlets, outlets, microchannels, microreservoirs and microvalves to ensure the effective delivery of analytes to the sensor, where analytes are recognized through physical or biochemical mechanisms. These recognition events are subsequently transduced into electrical or optical signals, which are transmitted by a microelectronics-based miniaturized and integrated flexible printed circuit board to user-terminal electronic devices, such as smartphones, tablets or computers, for readout.

Wearable flexible microfluidic biomedical sensors can be based on polymers or fibres. Polymer-based sensors are mainly made of elastomers, thermoplastics or hydrogels, and are packaged as patches, lenses or wristbands, whereas fibrous sensors are typically made of paper, thread, yarn or textile substrates.

Wearable polymeric microfluidic sensors

Polymer-based sensors show better processability, compatibility with current large-scale manufacturing techniques and a wider range of applications compared with fibrous sensors and typically have four layers: adhesive layer, microfluidic layer, sensing layer and encapsulation layer (Fig. 2a).

Adhesive layer. The adhesive layer, which is typically designed with inlets, directly adheres to the skin to sample biofluids. To ensure that the sensors closely and safely interface with human skin, the adhesive layer must be biocompatible, flexible, thin and skin adhesive. Commercial medical-grade acrylic adhesive films are often used for the adhesive layer owing to their strong adhesion (for example, ~5.7 N for ScapaHealthcare PC2723U (ref. 27) and 1.02 N for Tegaderm 3M (ref. 30)). The adhesive layer also includes openings to define the areas for biofluid collection and to allow biofluids to pass into the inlet region. To adapt to an aqueous environment, adhesive layers can be optimized with patterned vents to achieve robust bonding and reduce sweat corruption[31].

Microfluidic layer. The microfluidic layer typically consists of microchannels and microreservoirs made of elastomers (for example, polydimethylsiloxane (PDMS), thermoplastic polyurethane, poly(styrene-isoprene-styrene), styrene-ethylene-butylene-styrene), hydrogels or thermoplastics (for example, SU-8, polycarbonate, poly(methyl methacrylate), polystyrene, polyethylene terephthalate, polyimide, polyvinyl chloride, polyvinyl alcohol or polyethene). In particular, PDMS is biocompatible and transparent, and has a low Young modulus (~1–100 MPa)[32]; however, PDMS has low surface energy and its fabrication is complex and low throughput. By contrast, thermoplastic-based microfluidics have higher flexibility with regards to fabrication; in particular, SU-8 has abundant epoxy groups that facilitate strong bonding.

The microchannels typically have rectangular geometries with microscale width and height[33]. To create a microfluidic platform,

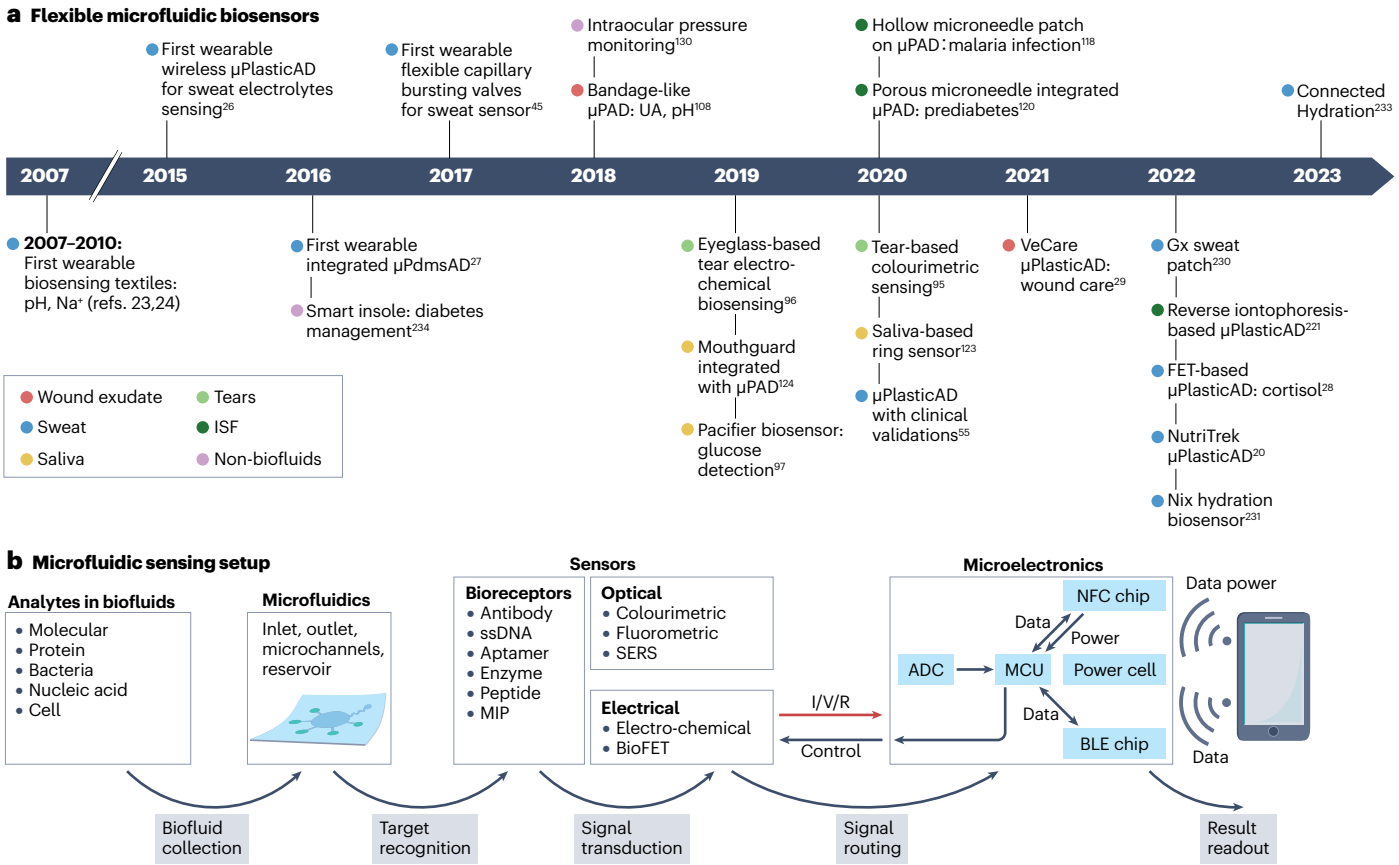


Fig. 1 | Flexible microfluidic biosensors for biomedical applications. **a**, Timeline of the development of flexible microfluidic biosensors. **b**, In a flexible microfluidic biosensing system, analytes are sampled from biofluids, delivered by a microfluidic channel and recognized by corresponding receptor molecules, which generates a signal that is transduced to provide a readout by microelectronics. **c**, Wearable microfluidic sensors for sweat, interstitial fluid (ISF), wound exudate, saliva, tears and non-biofluid analysis. μPAD, microfluidic paper-based analytical device; μPdmsAD, microfluidic polydimethylsiloxane-based analytical device; μPlasticAD, microfluidic plastic-based analytical device; ADCs, analogue-to-digital converters; BLE, Bluetooth low energy; BioFET, bio-field-effect transistor; FET, field-effect transistor; FPCB, flexible printed circuit board; I/V/R, current/potential/resistance; MIP, molecularly imprinted polymers; NFC, near-field communication; MCU, microprogrammed control unit; SERS, surface-enhanced Raman scattering; ssDNA, single-stranded DNA; UA, uric acid.

geometries, dimensions, volumes, materials and the physiochemical properties of the surface must be considered to minimize dead volume, exclude corner flow, and optimize capillary force and bursting pressure at each specific site[2,6]. The microfluidic layer can also be treated or modified to render it hydrophilic or hydrophobic in specific regions to control fluid flow[34].

Sensing layer. The sensing layer, which contains recognition and transducing elements, can either be combined with other layers or included separately within the flexible microfluidic device. Photoactive reagents, electrochemical receptors, including biomolecules (for example, DNA, proteins, antibodies, enzymes, aptamers), and electrodes made of low-dimensional materials (for example, graphene, goldnanoparticles) are used to sensitively and selectively sense the target[13]. The sensing layer should be selective, sensitive, reliable and stable, providing a low detection limit for either continuous monitoring or one-time use.

Substrate layer. The substrate layer provides the base and outer structural support for the sensors and usually contains outlets. Additional microelectronics may be included in or mounted on this layer. However, maintaining flexibility and device compliance, while accommodating discrete rigid electronic components, remains challenging.

Wearable fibrous microfluidic sensors

Fibrous flexible microfluidic sensing platforms are typically made of paper[35,36], thread or yarn[37], or textile substrates[38]. The fluid is driven by the capillary wicking properties of the fibres, the hydrophilic nature of the fibrous materials, and high-contrast hydrophobic and hydrophilic patterns. The regional hydrophobicity and wettability of fibres can be altered by surface modification techniques[35,36], including by coating of functional materials (for example, wax) or through chemical modification (amine group formation on cellulose paper)[39,40].

Microfluidic paper-based analytical devices (μPADs) are cheap, simple to fabricate and compatible with scalable cutting or printing techniques[41]; for example, lateral flow immunoassays, comprised of a sample pad, conjugate pad, analytical membrane and absorbent pad, can be made of commercial paper-based materials[42], such as glass fibres, nitrocellulose membrane, cellulose and other cellulose derivatives, to enable fluid collection and antibody immobilization[21]. Such devices are typically fabricated by 2D shaping or cutting of paper to define the channel and hydrophilic and hydrophobic patterning to direct the flow; 2D μPADs can also be transformed into 3D μPADs through folding and origami design to create microfluidic channels on different paper layers that can be connected for multiplexed and multistep assays[43,44].

Sampling and calibration

Time-sequential sampling. To capture biofluids and assess analytes sequentially in time, capillary bursting valves (CBVs)[45] and responsive materials[19,46] can be applied to open different channels at well-defined time points (Fig. 2b). By integrating CBVs with different colour-responsive reagents, located in separated reservoirs, multiple biofluid analytes (temperature, pH, chloride, glucose and lactate) can be assessed by colourimetric analysis to avoid interference of sample intermixing[47]. Furthermore, CBVs can be integrated with sweat-activated galvanic cells to precisely record temporal sweat composition fluctuation[48]. In addition, super-absorbent polymer-based valves[33] or stimuli-responsive hydrogels[19] can be implemented to control the flow for sequential colourimetric analysis; for example, an individually addressable, microheater-controlled active microvalve consisting of the thermo-responsive hydrogel poly(N-isopropyl acrylamide) can manage sweat collection and analysis in different compartments at relevant time points[19]. Moreover, a mechanical force can be applied to control the flow in the microfluidic module; for example, a finger-pressing reagent-leakage-proof check valve can be implemented to avoid backflow of the colourimetric reagents from the microreservoir[49]. Similarly, paper tabs embedded in the microchannel can be pulled for finger actuation to achieve on-demand capture and analysis of sweat[50]. Furthermore, mechanical stretching of the pinch valves and suction pumps can purge sweat into microchannels as a reset mechanism to coincide with new events[51].

Sweat rate and ISF extraction rate. The sweat rate can vary depending on individual passive perspiration conditions and stimulation, which can alter the composition of sweat owing to different secretion, reabsorption or partition mechanisms of specific analytes[52,53]; for example, large molecules, such as cytokines and metabolites, have higher concentrations during active sweating (high sweat rate)[54]. The amount of extracted interstitial fluid (ISF) can also fluctuate owing to individual differences and stimulation. Therefore, the sweat rate and ISF extraction rate should be considered when calibrating the concentration of the analyte.

The sweat rate can be estimated by colourimetric or electrical measurements using microfluidic channels. Colourimetric sweat rate measurement relies on the filling rate of a visualization agent that is mixed with sweat at the inlet of the microfluidic channel[55]. Alternatively, the sweat rate can be electrically measured by assessing the admittance or resistance change between microfluidic-connected electrodes[56]. Thermometers can also be incorporated into the microfluidic channels to measure the sweat flow rate[57]. To calibrate the influence of the sweat rate on target monitoring, a sodium ion sensor can be implemented to potentiometrically monitor sweat levels to compensate for variation[20]. However, even if the sweat rate can be precisely captured, the complex relation between sweat rate and sweat composition as well as other interference factors, such as pH, temperature and motions, make an accurate calibration in the quantitative analysis (for example, electrochemical evaluation of lactate and glucose) of sweat samples challenging. To calibrate the influence of the ISF extraction rate, sodium extraction rates can be used to indicate the ISF extraction rate; for example, a flexible electrochemical glucose sensor and sodium sensor can be applied to simultaneously monitor glucose and sodium concentrations in the extracted ISF in situ[58]. The corrected blood glucose concentration can then be obtained based on differential correction models obtained from the two concentrations.

Matrix, evaporation, mixing and aqueous conditions. The composition and concentration of analytes in the collected biofluids can also be influenced by the evaporation of biofluids[59], aqueous conditions[31], biological materials, and contamination and chemicals from the source or environment. Although the confinement of microfluidic channels can prevent evaporation, biofluids may evaporate through the outlets and microchannel materials, which can be addressed by using specially designed small outlets, ensuring dead volume near the outlet and applying non-permeable elastomers[31].

Flexible microfluidic devices, in principle, isolate biofluids from the environment; however, reagents of different channels may be

Table 1 | Microfluidic-based flexible biomedical biosensors

Analytes	Clinical relevance	Merits and challenges	Sampling	Microfluidic materials and engineering strategies	Transducing principles	Applications	Innovations
Sweat: skin patch sensor							
Ions, metabolites, nutrients, hormones, neurotransmitters and proteins	Electrolyte loss and hydration state during exercise; liver and kidney function; diabetes management; mental and neural health; stress and nutrition level	**Merits:** non-invasive; diverse biochemical information; easy to access **Challenges:** metabolic lag; low concentrations of biomarkers; uncontrolled sweat flow; evaporation and contamination; limited operation conditions (for example, difficult to measure during sleeping or at rest)	Capillary force, natural pressure	PDMS, soft lithography	Colourimetric	Sports: monitoring of total sweat loss, pH, lactate, chloride, glucose	The first wearable, colourimetric, flexible microfluidic sensor with multifunctions[27]
			Capillary force, natural pressure	SIS, soft lithography	Colourimetric	Sports: monitoring of chloride, local sweat loss (and sweat rate), skin temperature	Designed for aquatic conditions[31]
			Capillary force, natural pressure CBVs	PDMS, soft lithography	Colourimetric	Sports: monitoring of sodium, chloride, potassium, calcium, magnesium, copper, iron	Sweat-triggered galvanic stopwatches for time-dependent analysis[48]
			Capillary force, natural pressure CBVs	PDMS, soft lithography	Colourimetric	Nutrients: monitoring vitamin C, calcium, zinc, iron	Colourimetric nutrients monitoring and delivery[61]
			Capillary force, natural pressure	PDMS, soft lithography	Colourimetric and electrochemical	Sports: monitoring of sweat rate and sweat loss, pH, lactate, glucose, chloride	Integration of biofuel cell-based glucose and lactate monitoring with general sweat monitoring[151]
			Capillary force, natural pressure	Roll-to-roll, laser and die cutting	Colourimetric	Sports: monitoring of sweat rate, chloride	Validated in 312 athletes under various conditions[55]
			Capillary force, natural pressure CBVs	PDSM, soft lithography	Colourimetric	Sports: monitoring of sweat loss, pH, temperature, lactate, chloride, glucose	Colour reference markers to avoid light interferences for quantitative analysis[47]
			Capillary force, natural pressure, electrowetting valve	Polyimide, pressure-sensitive adhesive and PET, laser cutting	Electrochemical	Physiological stress, diabetes (monitoring of cortisol and glucose)	Accurate detection of cortisol with absorbent pad for sweat evaporation and electrowetting valve for detection triggering[60]
			Responsive hydrogel valve, mechanical force	PET and double-sided 3M tape, laser cutting	Electrochemical	Sports: monitoring of glucose, lactate	Active biofluid management by thermo-responsive hydrogel valves for contextual analysis[19]
			Capillary force, natural pressure	PET and double-sided tape, laser cutting	Electrochemical	Sports: monitoring of glucose, lactate, choline	Sensors with strain-isolated pathway to avoid mechanical interference[63]
			Capillary force, natural pressure	PDMS, 3D printing mold and transfer printing microchannels	Electrochemical	Sports: monitoring of potassium	Wireless battery-free sensitive detection of potassium[219]
			Capillary force, natural pressure	Adhesive and PET or polyimide, laser cutting	Electrochemical	Sports: monitoring of lactate, sodium, potassium, pH	High-throughput laser-engraved microfluidic sweat sensor[100]

Table 1 (continued) | Microfluidic-based flexible biomedical biosensors

Analytes	Clinical relevance	Merits and challenges	Sampling	Microfluidic materials and engineering strategies	Transducing principles	Applications	Innovations
Sweat: skin patch sensor (continued)							
			Iontophoresis	Adhesive, PET and polyimide, laser cutting	Electrochemical	Nutrition and metabolic syndrome: monitoring of all essential amino acids, vitamins	Continuous detection of multiple biomarkers related to nutrition and metabolism with regeneration capacity[20]
			Super-absorbent polymer valve	PDMS and PET, soft lithography	Electrochemical	Mental disorders: monitoring of pH, chloride levodopa, sweat rate	Detection of resting sweat[18]
			Capillary force, natural pressure	PDMS, soft lithography	Electrochemical	Sports: sweat loss, sweat rate, sodium and chloride	Wireless, battery-free digital tracking of sweat loss with electrodes[56]
			Capillary force, natural pressure	PDMS, soft lithography	Optical	Sports: monitoring of urea, lactate, pH	In situ and continuous SERS sensing[153]
			Iontophoresis	PDMS	Electrochemical	Diabetes: monitoring of glucose	Does not require exercise[220]
ISF: microneedle sensor							
Ions, glucose, urea, vancomycin, cortisol, insulin, haemoglobin, cytokines, albumin, antibodies	Diabetes management, therapeutic drug monitoring, infections, inflammatory disorders	**Merits:** similar analyte composition and concentration to blood serum **Challenges:** low volumes, limited sampling rate, variability in multisite measurements, difficult to access	Capillary force	Bandage tape, laser cutting	Colourimetric	Virus detection: antigen monitoring	Hollow microneedle for ISF extraction[118]
			Reverse iontophoresis, capillary force	PET, laser engraving	Electrochemical	Cystic fibrosis screening: monitoring of chloride, calcium	Integration of RI and microfluidic channel[221]
Saliva: pacifier and mouthguard sensor							
Electrolytes, immunoglobulins, proteins, enzymes, mucins	Oral diseases, diabetes, renal diseases, hepatitis, neurodegenerative diseases, immunodeficiency diseases	**Merits:** large volume; contains various biomarkers **Challenges:** harsh environments and high requirements for biocompatibility	Capillary force	PDMS, soft lithography	Electrochemical	NICU: monitoring of sodium, potassium	Hydrophilic channel that facilitates the flow of saliva[125]
Tears: contact lens sensor							
Electrolytes, proteins, lipids, mucins	Dry eye disease, metabolism, ocular and systemic diseases	**Merits:** similar composition to blood; variety of biochemical information **Challenges:** low sample volumes and rate; extracted from the eyeball, which is sensitive to mechanical and chemical stimulation	Capillary force	Fluorosilicone acrylate, laser cutting	Colourimetric	Ocular health: monitoring of pH, glucose, protein, nitrites	Multiple colourimetric sensors integrated into contact lens[95]
			Capillary force	Paflufocon/silicone hydrogel, laser cutting	Colourimetric	Dry eye severity: monitoring of pH, sodium, potassium, calcium, magnesium, zinc	Full-spectrum electrolyte integration[126]
			PDMS	PDMS, soft lithography	Physical	Glaucoma: pressure monitoring	Implantable microfluidics pressure meter[129]
Wound exudate: wound dressing or bandage sensor							
Electrolytes, metabolites, proteins, cells, microorganisms	Wound assessment and management	**Merits:** abundant in important biochemical analytes **Challenges:** complex composition	Capillary force	SU-8, photolithography	Electrochemical	Chronic wound infection: monitoring of temperature, pH, IL-6, IL-8, TNF, TGFβ1, *Staphylococcus aureus*	Integration of immune sensors[29]

CBV, capillary bursting valve; ISF, interstitial fluid; NICU, neonatal intensive care unit; PDMS, polydimethylsiloxane; PET, polyethylene terephthalate; RI, reverse iontophoresis; SERS, surface-enhanced Raman scattering; SIS, styrene-isoprene-styrene; TGFβ1, transforming growth factor-β1; TNF, tumour necrosis factor.

mixed, previous biofluids may be retained or mixed with fresh biofluids, and contaminants may enter the device from the inlet interface. Mixing of reagents may be prevented by designing channels with an electrowetting valve[60] and by programming fluid control components, such as CBVs, to time-sequentially uptake biofluids and detect analytes in individual channels without cross-contamination[61]. Furthermore, passive fluid-flow pumping methods can ensure biofluid refreshment in the microchannels for real-time measurement of analytes. To minimize chemical and biological contamination (for example, cosmetics, microorganisms, dead skin cells) from the inlet interfacing with a biological surface, such as the skin, the surface should be cleaned before they come in contact with flexible microfluidics. Interferences from the sample matrix can be avoided through pre-separation and filtering by microfluidic-based affinity materials and filtered or suppressed by highly selective recognition elements.

Wearable sensing challenges

Strain. Body movement-induced mechanical deformation of flexible microfluidic sensors can affect the stability of microfluidic flow and their sensing ability[62,63]. In particular, motion-induced strains can alter the geometry of the flexible microchannel and affect the flow, thus influencing flow rate, on or off state of flow, sensing abilities and microfluidic functions such as filtering capabilities. Strain-induced disturbance of the solid–liquid electrochemical interface, variation of the 3D structure of the receptor and deformation-induced microcracks on non-stretchable functional layers (for example, electrode

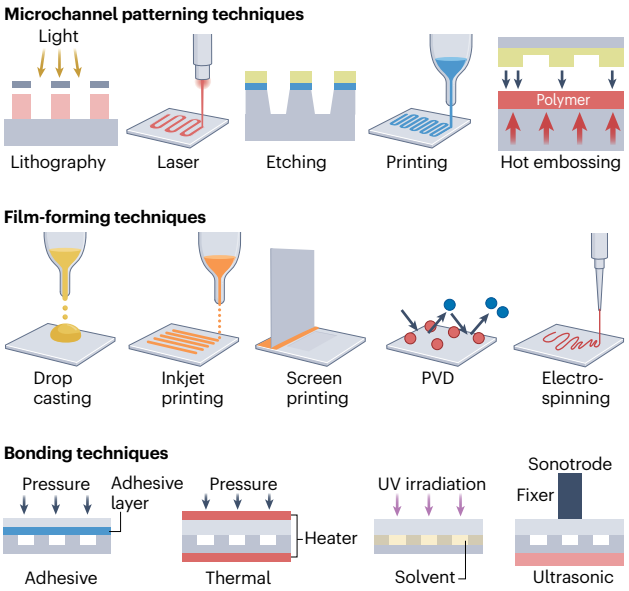
Box 1

Fabrication of wearable flexible microfluidic sensors

The manufacture of wearable flexible microfluidic sensors involves the patterning of flexible microchannels and the fabrication of functional layers for flexible sensors[222] (see figure). Depending on the material, flexible microchannels can be patterned by lithography, laser cutting or engraving, stamping, etching and printing. Polydimethylsiloxane (PDMS)-based flexible microchannels are mainly fabricated by soft lithography[223]; here, patterns are replicated from photolithography or 3D-printed templates. Thermoplastic-based flexible microchannels are typically produced by laser cutting, hot embossing, etching or 3D printing[224]. Laser cutting can be used to fabricate cut-through channels in a polymer film, which is then sandwiched by and bonded with two polymeric layers to create microfluidic channels. Fibrous flexible microchannels are engineered by wax printing, physical deposition, chemical modification or laser cutting[43,108,136].

Films of functional layers for the design of flexible sensors can be fabricated by printing, drop casting, spin coating, and physical or chemical deposition. The sensing layer of electrochemical sensors consists of conductive and recognition materials. Conductive materials for the fabrication of electrodes and interconnects are designed by physical vapour deposition (PVD) of gold or carbon, screen or inkjet printing of carbon inks, or laser engraving of graphene[100]. Recognition materials of electrochemical sensors, such as enzymes or molecularly imprinted polymers, are typically drop-casted, electrochemically deposited or polymerized on the electrodes.

To integrate different layers or bond polymeric films for microchannels, different bonding strategies can be applied. PDMS bonding is achieved by chemical modification; for example, by grafting of polar hydroxyl groups using O_2 plasma or corona discharge treatment, or through modification of amino groups by (3-aminopropyl) triethoxysilane or epoxy groups by 3-glycidoxypropyltrimethoxysilane[225]. Polymeric films are bonded by chemical modification, adhesive bonding, thermal fusion, solvent treatment or ultrasonic welding[226]; here, adhesive bonding is the most straight-forward process, using a commercial UV adhesive (for example, Slink 80801) and UV irradiation, pressure-sensitive



adhesives (for example, ARcare 90445), or adhesive agents (for example, chitosan–polydopamine). Thermal fusion may lead to temperature-induced deformation, which may change the pattern of the microchannels. In solvent bonding, a compatible solvent achieves high bond strength, preventing thermal-induced microchannel deformation[227].

To produce microfluidic-based sensors at a large scale, roll-to-roll processing of polymeric rolls can be integrated with screen-printing technologies[228,229] and laser die cutting[55], allowing the rapid (1-minute) fabrication of electrochemical and colourimetric devices. Laser-induced graphene-based technologies have also been used to rapidly produce prototypes with multiple electrochemical sensors[20,100].

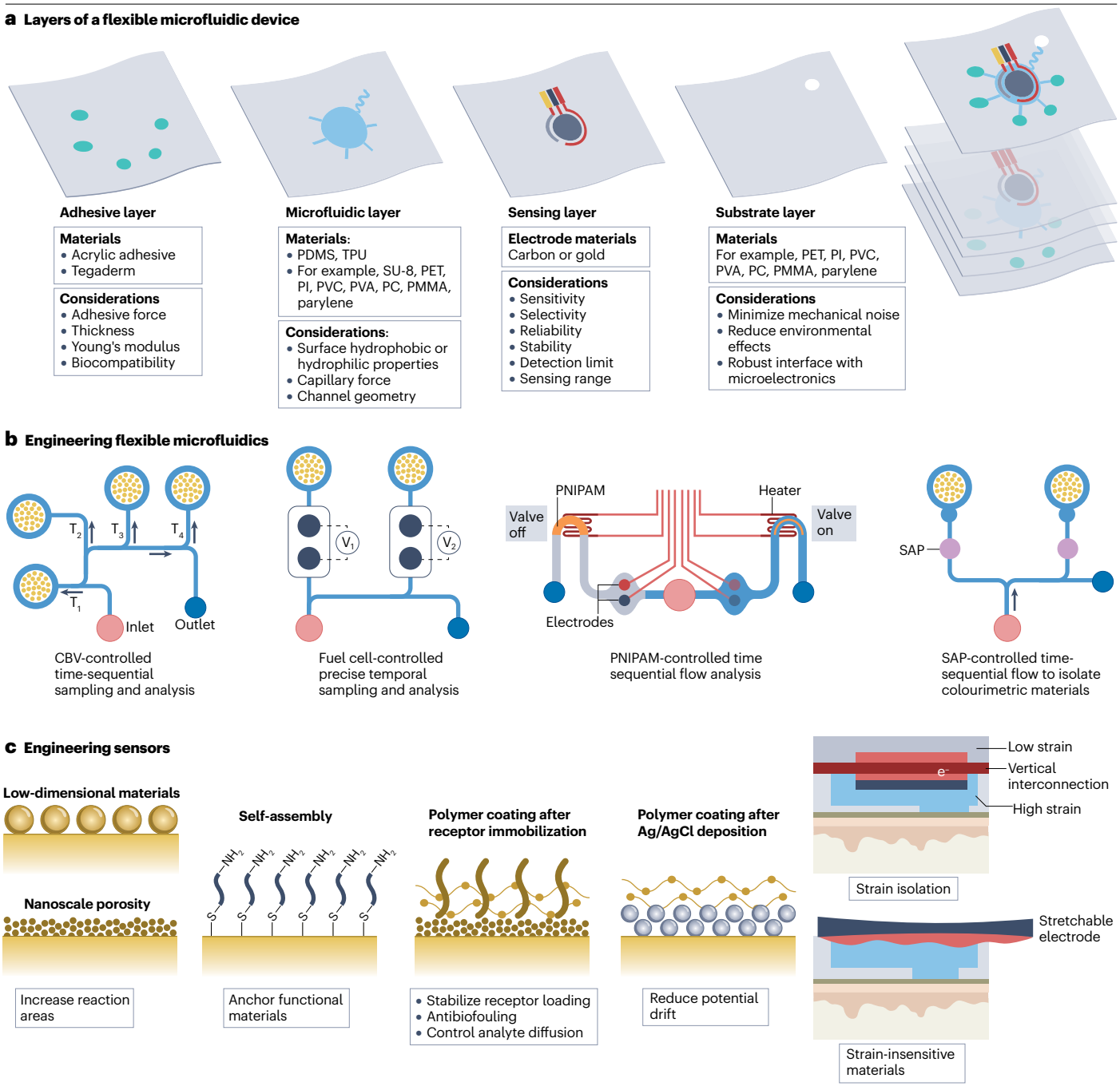


Fig. 2 | Building blocks of flexible microfluidic biosensors. a, Different layers of a flexible microfluidic device. **b**, Materials and engineering strategies for flexible microfluidics. Capillary bursting valves (CBVs) can control time-sequential sampling and analysis. Fuel cells can be introduced to provide precise temporal sampling and analysis. Super-absorbent polymer (SAP)-based valves can control time-sequential flow to isolate colourimetric materials to prevent cross-contamination. Stimuli-responsive hydrogels, such as poly(*N*-isopropyl acrylamide) (PNIPAM), can be applied to control time-sequential flow analysis. **c**, Materials and engineering strategies for sensors. To increase the amount of active reaction sites, the electrode can be modified with low-dimensional materials (for example, by depositing nanogold, carbon nanotubes or graphene) or engineered with nanoscale, microscale or porous structures on the surface. To stably anchor functional layers on the electrodes, molecules with functional groups can be self-assembled on the electrodes for grafting. Working electrodes modified with functional layers can also be coated with a polymer to stabilize the functional materials, limit the diffusion of the analyte to the reaction sites in case of overload and prevent fouling. Reference electrodes can be coated by a polymer layer, such as polyvinyl butyral, to reduce potential drift and ensure the correct reference potential. To address strain interference, strain-isolation and strain-insensitive strategies can be applied to isolate low-strain and high-strain areas. Alternatively, stretchable electrodes can be used. PC, polycarbonate; PDMS, polydimethylsiloxane; PET, polyethylene terephthalate; PI, polyimide; PMMA, poly(methyl methacrylate); PVA, polyvinyl alcohol; PVC, polyvinyl chloride; TPU, thermoplastic polyurethane.

layer, receptor layer) can further result in signal drift, performance deterioration and signal disruption[64,65].

Strain-insensitive and stretchable electrodes can account for motion-induced strain[66,67] (Fig. 2c); for example, a stretchable electrode made of nanoporous gold and 3D micropatterned PDMS, used in a flexible microfluidic electrochemical glucose monitoring system, can achieve 30% strain tolerance without signal deterioration[68]. However, swellable polymer inclusions in stretchable electrodes may cause instability in electrical signals during long-term measurements[69]. Moreover, recognition elements, which typically contain rigid elements, may not withstand deformation. Alternatively, biomarker signals can be delivered through a strain-isolated region in the microfluidic device[63] (Fig. 2c). The vertical interconnection and out-of-plane signal transmission eliminate the effects of high-frequency body movements and enable stable reading. To avoid any impact of strain on sensors, non-stretchable islands can be constructed in which sensing modules are protected from strain[70].

Temperature and pH. Variable working conditions, such as pH and temperature, can also affect sensor performance by altering enzyme activity, redox label activity, or the chemical structure and properties of the materials. To correct for pH and temperature alterations in real time, multiplexed sensors can be designed that integrate pH (ref. 28) and temperature sensors[71,72]. However, prolonged exposure to high temperature, alkalinity or acidity that exceed the capacity of the functional materials may cause the irreversible destruction of bioreceptors, leading to permanent damage to the sensor. Alternatively, stable functional materials can be applied that withstand a wide pH and temperature range[73].

Biofouling. Biofouling, which is caused by the non-specific binding of proteins, macromolecules and cells to the sensor surface, can impede the diffusion and binding of target analytes and lead to a gradual decrease in sensing performance. Biofouling should be particularly avoided for implantable or minimally invasive sensors, long-term continuous sensors, and sensors working in protein-abundant surroundings (for example, oral cavity). Anti-biofouling surface protection can be designed to mitigate biofouling without affecting target diffusion; for example, sensors can be coated with anti-biofouling hydrogels, polymeric coatings (such as polyethylene glycol), zwitterionic coatings, Nafion, polyvinyl chlorides or serum albumin to alter their surface hydrophilicity, charge state or porosity, thereby preventing the adsorption of molecules through repulsion or size exclusion[10,74–76].

Flexible microfluidics

Functions of flexible microfluidics

Flexible microfluidics can improve the functionality of wearable sensors by enabling and improving various functions, including analyte collection, transportation and separation, in situ analyte analysis, fluid flow direction and speed control, and microfluidic resetting or sensor regeneration (Fig. 3a).

Analyte collection, transportation and separation. Microfluidic platforms enable the collection of biofluids at low volumes (nanolitre, microlitre), transportation of reagents or analytes to the detection site, and rinsing and separating of unwanted compositions. In a typical lateral flow affinity sensor, flexible microfluidic channels collect biofluids into the sample pad, convey the fluid to the conjugate pad, where analytes interact with labelled 'detection' bioreceptors, and transport the analyte–bioreceptor complex being detected to the test line, where it interacts with 'capture' bioreceptors to form a sandwich format, resulting in a signal[21]. In sensors based on catalytic reactions, including ionophore–ion interactions, direct redox reactions, direct or displacement binding between receptors and analytes, and conformation changes of receptors upon target binding, flexible microfluidics are typically used for rapid biofluid collection, accumulation and transport to the detection site[20,28]. Flexible microfluidics can also be applied to exclude or separate unwanted components in the biofluid matrix or fluids, facilitating a high sensing performance. To rinse unbound reagents and dispose of waste, the washing buffer can be moved from the wash chamber to the sensing chamber through finger touch[77,78]. Microfluidic devices can also be used to sort, filter, and separate cells, bacteria, particles and biomolecules[6,79]; however, owing to their complex set-up, the requirement of stable operating environments and external flow control devices, and frequent motion-induced deformations, such devices are typically not used in wearable microfluidic sensors. Nevertheless, strain-isolated flexible microfluidic channels could be integrated into wearable flexible fluidic sensors for the pretreatment of biofluids and to improve sensing.

Analyte analysis. Flexible microfluidics can be applied for sensing without requiring prefilled sensing reagents. The thermal and electrical properties of the fluid in the microfluidic channels can be exploited to sense certain targets; for example, the relative conductivity of fluidic channels compared to that of the reference channels during the filling process can provide information about the fluid volume, flow rate and electrolyte concentration[56]. By measuring the temperature difference between two sites of a microfluidic channel, each equipped with a thermometer and a heater in between, the flow velocity can be calculated[57]. In addition to sensing analytes through fluid flow in microchannels, steady fluid sealed in elastomers can be used for sensing; for example, liquid metal and ionic liquids can be injected into the elastic microchannel to function as resistor and capacitor, respectively, to sense mechanical loadings such as pressure and strain[80,81].

Fluid flow direction and speed control. The microchannels of flexible microfluidics can be engineered so that capillary force[45,47,61], hydrophobic or hydrophilic forces[34,46], passive or active mechanical loads[51,82], and internal negative and positive pressures[20,51] can be applied to control fluid flow direction and speed. To transport fluid directionally and passively, chemical and topological engineering strategies can be applied by constructing chemical, roughness, stiffness, or curvature gradients or asymmetric structures[83]. Moreover, CBVs[61], super-absorbent polymer valves[46], stimuli-responsive hydrogel valves[19] and hydrophobic valves[34] can control the flow to achieve time-sequential analysis. Time-sequential colourimetric sensors, facilitated by multi-channels and valves, may prevent reagent contamination[47], and multistep bioaffinity assays, particularly immunoassays, can exploit microfluidics and valves to temporally introduce reagents for rinsing or reaction[77,78].

Microfluidic resetting or sensor regeneration. As previous biofluids may interfere with subsequent data[51] or impede the collection of new samples for continuous monitoring[56,82], microchannel inclusions need to be cleaned before new testing events. Microchannels can be reset using a strain-actuated elastomeric suction pump and elastomeric pinch valve[51], or manually by pressing the suction cup[82], enabling repeated longitudinal tests and continuous electrochemical monitoring by propelling regeneration chemicals or solvents[10] to the sensing site to regenerate recognition sites.

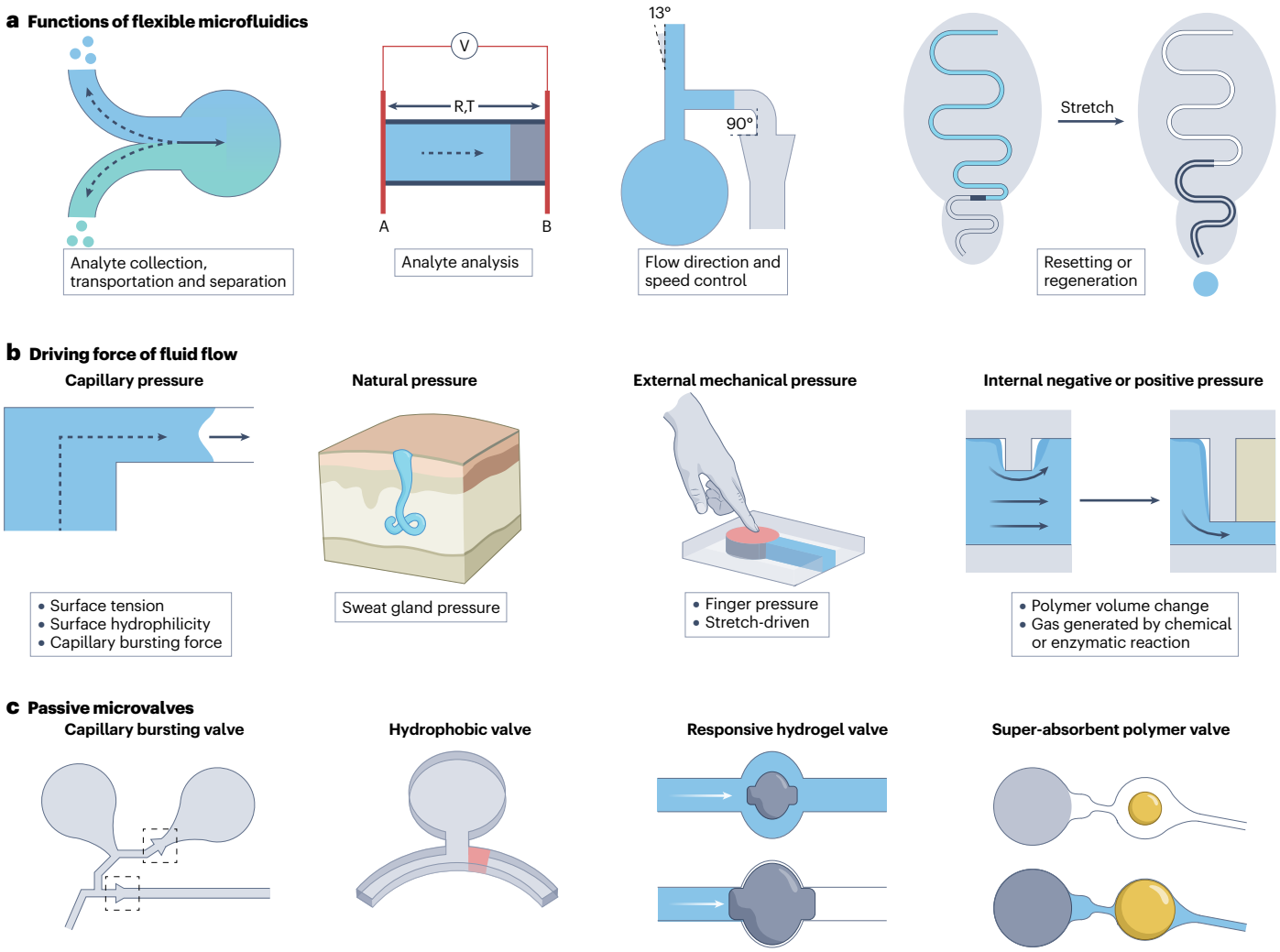


Fig. 3 | Functions of flexible microfluidics. a, Functions of microfluidics for sensors include analyte pretreatment, analysis through measurement of the resistance (R) or temperature (T) difference between two ends (A and B) of the fluid, control, and resetting or regeneration. **b**, Liquid handling forces include capillary pressure, natural pressure, external mechanical pressure, and internal negative or positive pressure. **c**, Passive microvalves include capillary bursting valves, hydrophobic valves, responsive hydrogel valves and super-absorbent polymer valves. V, voltage.

Driving force

Various forces can be exploited in flexible microfluidic platforms to control fluid flow, including natural sweat gland pressure, capillary pressure, internal negative or positive pressure, external mechanical pressure, and other forces (Fig. 3b).

Natural sweat gland pressure. Natural sweat gland pressure can be used to directly push sweat into a microfluidic channel. The eccrine gland can generate a pressure of up to 70 kPa, which can be increased to over 72 kPa through chemical stimulation[54].

Capillary force. Capillary pressure is exploited in most microfluidics based on polymers, paper, yarn, thread and textiles. The capillary channels in polymeric microfluidics are typically rectangular microchannels, whose capillary pressure is calculated by the Young–Laplace equation[84], which takes into account the surface tension of the liquid, the height and width of the microchannel, and the contact angles of the liquid on the wall. The capillary pressure can also be adjusted by fluid composition, surface chemical properties and topography[83]. By contrast, in fibrous microfluidics, the capillary channels are the voids between adjacent fibres of yarns or the high-contrast hydrophobic–hydrophilic patterns in textiles and papers. The maximum wicking height can be calculated by the Washburn equation and is related to pore size of the yarn, surface tension of the liquid, and the advancing contact angle of the liquid on the solid[85].

Internal negative or positive pressure. Internal negative or positive pressure can be created using polymers or hydrogels that respond to thermal, optical, electrical or chemical stimuli[86]. These hydrogels or polymers can work as micropumps or microvalves by shrinking or expanding their volumes[19,46]. Chemical or enzymatic reactions that generate gas can also be used to pump liquids; for example, hydrogen

peroxide[87] and sodium bicarbonate[51] can be applied to generate oxygen and carbon dioxide, respectively, to drive flow.

External mechanical pressure. External mechanical pressure, such as finger pressure[88] and stretching[51], can be used to control fluid flow. Finger-pressing can propel the washing buffer from the washing chamber to wash away unbound reagents in the sensing chamber and decrease the sensing limit[78]. In addition, flexible microfluidics can be stretched to draw fluids out and reset channels through pinch valves and suction pumps[51].

Other forces. Gravity, osmosis, electrowetting and diffusion are often applied in microfluidics to drive fluid flow[89]. Gravity-driven microfluidics only require height differences between two liquid reservoirs to propel fluid flow, allowing simple operation, However, gravity-driven microfluidics are difficult to integrate into wearable platforms and they produce long-term continuous flow. Alternatively, osmotic pressure can pump biofluid to a region with higher solute concentration (for example, hydrogels with a high osmolyte concentration)[90]. Moreover, electrowetting on a dielectric can aid in controlling fluid flow in a microchannel using a low voltage to initiate the sensing of analytes[60].

Passive micropumps and microvalves

Passive forces, such as capillary forces, are commonly used for microvalves and micropumps in flexible microfluidic platforms. Capillary passive micropumps and microvalves, including capillary pumps, CBVs and hydrophobic valves, are often applied in wearable devices owing to their simplicity (Fig. 3c). Although various types of passive valves, including flap valves[91], diaphragm valves[91] and elastic snap-through valves[92], as well as osmosis-based hydrogel pumps[90] have been developed, capillary force remains the most commonly applied modality in flexible microfluidics.

Capillary pump. Contact angle, dimensions and final capillary pressure need to be considered in the design of capillary pumps. A contact angle of less than 60° ensures a high capillary pressure and prevents defect points that can disrupt the entire system. The contact angle can be reduced by applying hydrophilic or plasma-treated materials, such as paper, textile, thread, elastomers and plastics[34], for the channel walls. PDMS-based channel walls typically exhibit uniform contact angles, whereas plastic-based channels with adhesives or other heterogeneous microfluidics may have different contact angles on different walls. Rational design of the channel dimensions is thus necessary to avoid corner flows or disruption of the microfluidic platforms[33].

Capillary bursting valve. Capillary force can be used in the design of CBVs[45] to time-sequentially direct fluid flow to different channels for the temporal analysis of multiple analytes[45,47,61]. To create CBVs, the channels can be engineered with different bursting pressures[35]. Importantly, the bursting pressure should exceed the pressure difference between the fluid-filled channel and the front, unfilled channel to allow the fluid to advance into the channel. The bursting pressure (BP) can be calculated by the Young–Laplace equation[93]:

$$\mathrm{BP} = -2\gamma\left[\frac{\mathrm{COS}\theta_l^*}{w} + \frac{\mathrm{COS}\theta_A}{h}\right] \quad (1)$$

where γ is the surface tension of the liquid, θ_A is the contact angle of the channel, θ_l^* is $\min\{\theta_A + \beta, 180°\}$, β is the diverging angle of the channel, and h and w are the height and the width of the diverging section, respectively[45]. The bursting pressure is determined by the physicochemical properties of the materials of the diverging outlet channels (for example, liquid surface tension and contact angle of walls) and their diverging geometry (for example, width, height and diverging angle). A small width and low height of microfluidic channels correspond to a high bursting pressure[84], and fluid typically goes through the channel with a low bursting pressure. CBVs allow control of sequential flows but require a complex fabrication process involving lithography.

Hydrophobic valve. Hydrophobic valves in microchannels are created by dividing the channel into hydrophobic and hydrophilic regions, which are also controlled by capillary force. On a hydrophilic and wettable surface, the concave liquid–air interface with negative capillary pressure can wick liquid into the channels. By contrast, a convex liquid–air interface with positive capillary pressure pushes the liquid out of the channel. Thus, the hydrophobic region creates a pressure barrier that blocks liquid flow from the hydrophilic region to the hydrophobic region. Hydrophobic valves can be created by subjecting the exposed hydrophobic region to ozone, plasma, or UV light or by treating the exposed hydrophilic region with silanes[34,46,84]. Of note, surface roughness and chemical composition determine surface hydrophilicity and hydrophobicity.

Biosensing with wearable flexible microfluidics

Biofluid sampling

Biofluids, such as sweat, saliva, ISF and wound exudate, contain valuable biomarkers[13], such as glucose, lactate, cortisol, inflammatory biomarkers and DNA, with concentrations similar to those in blood. To analyse biomarkers in these biofluids, various flexible microfluidic sensors have been developed in the form of skin patches[94], wound dressings[29], contact lenses[95], eyeglass accessories[96], pacifiers[97] and mouthguards[98] (Fig. 4a). However, such biofluids can be challenging to sample and analyse owing to their complex environment (for example, the oral cavity contains bacteria and food residues), inaccessible sites (for example, ISF is located in subdermal regions)[99], and small or unevenly distributed sample volumes (for example, varying sizes of a wound).

Sweat. Sweat is an easily accessible biofluid and can be directly sampled by wearable patch sensors[18,20,100]. Although convenient, such a collection method faces challenges, including sample mixing and evaporation as well as a low sweating rates at thermoregulating conditions (~10–100 nl $\mathrm{min}^{-1}\,\mathrm{cm}^{-2}$)[18]. Although exercise can be used to stimulate sweating[29,101,102], this approach is not suitable for all wearers. Alternatively, external stimulation, such as electrical iontophoresis[20,103], or chemical stimulants, such as pilocarpine[103] and carbachol[104,105], can locally accelerate the sweating rate. To maximize sweat collection efficiency and reduce sweat evaporation, microfluidics with multiple inlets can be interfaced with sweat pores[106] or microfluidics can be integrated with stimulants[20]. To increase sweat uptake efficiency without stimulation and to collect sweat under resting or thermoregulated sweating conditions, hydrophilic fillers covered with a hydrogel film can be placed at the inlet of the microfluidic channel. The filler enhances sweat collection by occupying the dead volume in the collection well and by drawing sweat as soon as it is secreted, thus contributing to rapid sweat accumulation and reliable sensing at a low sweating rate[18] (Fig. 4b).

Device and sampling strategies

Flexible microfluidics and sensors

Signalling transduction and readout

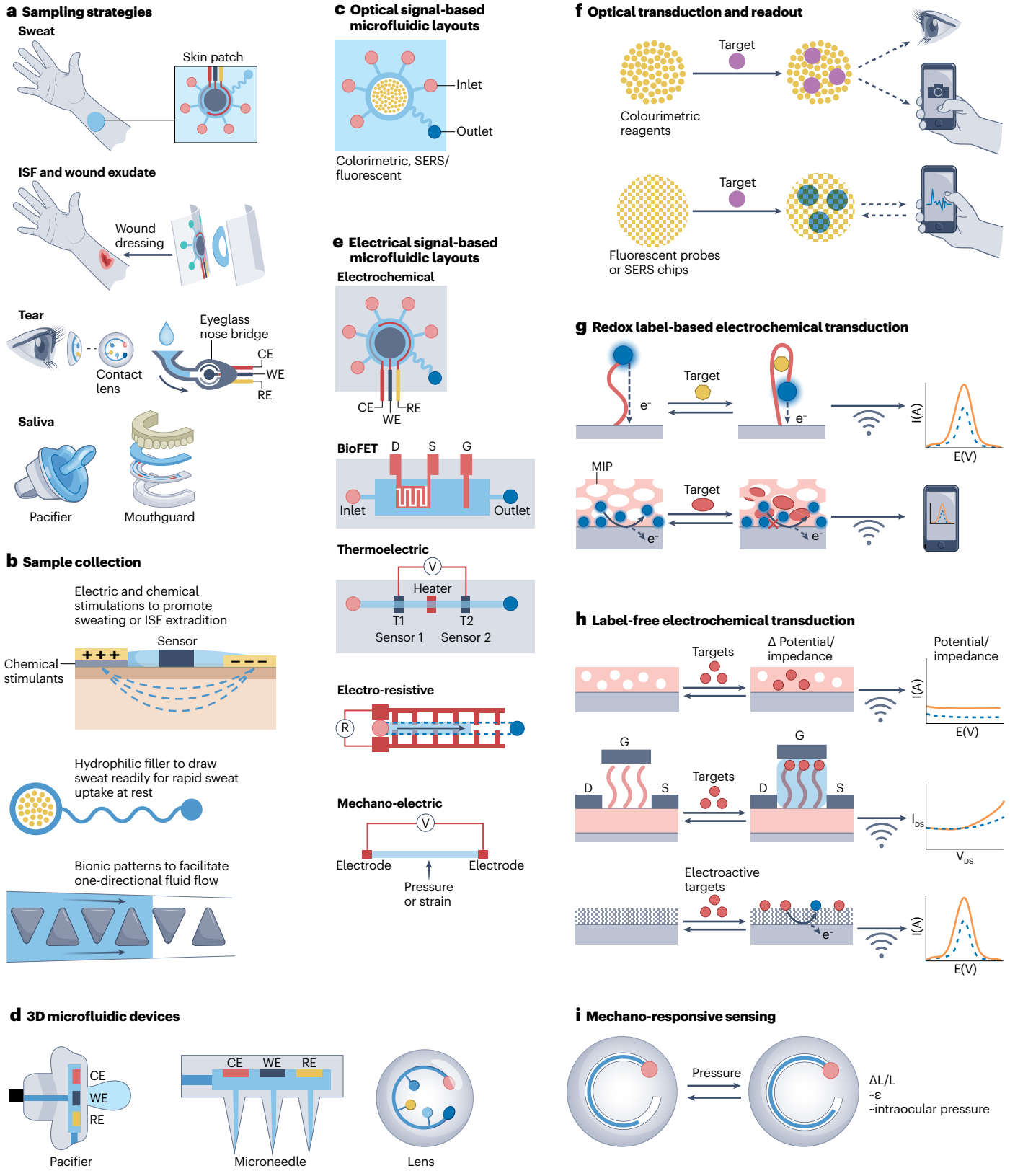


Fig. 4 | Sampling and sensing strategies of flexible microfluidic sensors. **a**, Flexible microfluidic sensor formats for various biofluids. The miniaturized skin patch allows sweat analysis[20,27]. A flexible patch[94] with a biomimetic passive microfluidic collector can be integrated into wound dressings[29] for wound exudate monitoring. A smart contact lens[95] and a microfluidic device integrated into an eyeglass nose-bridge pad[96] to enable monitoring of tears. Pacifiers[97] and mouthguards[98] can be designed for saliva analysis. **b**, Iontophoresis, reverse iontophoresis, biochemical stimulants and passive microfluidic structures, including hydrophilic fillers and bionic patterns, can facilitate sample uptake in microfluidic sensors. **c**, Optical signal-based microfluidic layouts contain reservoirs that are preloaded with colourimetric reagents, surface-enhanced Raman scattering (SERS) chips or fluorescent probes. **d**, 3D microfluidic devices can be designed by configuring out-of-plane microfluidic channels and sensing elements in a microfluidic pacifier, microneedle patch or eye contact lens. **e**, Electrical signal-based microfluidic layouts. Biochemical targets can be analysed by electrochemical microfluidics or a bio-field-effect transistor (BioFET) system. Physical targets are typically analysed by thermoelectric microfluidic devices with thermometers and heaters, electro-resistive microfluidic devices with an interdigital electrode connected by fluids, or electro-mechanical devices with closed channels that are electrically connected with leads. **f**, Optical transduction and readout. Optical signals from chemiluminescence reagents can be qualitatively captured by the naked eye or semi-quantitatively by cameras, whereas fluorescent probes and SERS chips require both an excitation light source and a photodetector for signal detection. **g**, Redox label-based electrochemical transduction. Molecule-selective receptors, such as antibodies, nucleic acids or synthesized molecularly imprinted polymers (MIPs), can incorporate redox labels to transduce target recognition information to electrical signals. **h**, Label-free electrochemical transduction. Label-free transducing techniques include electrochemical impedance, field-effect transistors (FETs) or nanostructures. The target selectively interacts with modified electrodes (for electrochemical impedance spectroscopy transduction and nanostructures based on non-enzyme sensing) or FET channels, altering the interface conditions, which causes signal differences. In FET transduction, the surface potential of the gate membrane changes with receptor-target adsorption, resulting in a measurable current shift between source and drain. In electrochemical impedance spectroscopy transduction, selective binding of the target and receptor on the functionalized electrode surface results in an impedance change; for nanostructure-based non-enzyme sensors, the Faraday current increases with transferred electrons produced by the redox reactions of the analyte. **i**, Mechanoresponsive sensing. Mechanical force (for example, intraocular pressure-related strain (ε) on a contact lens) can induce the deformation of a microchannel, resulting in physicochemical changes (for example, relative length change ($\Delta L/L$)) of trapped fluids. CE, counter electrode; D, drain; G, gate; I, current; ISF, interstitial fluid; S, source; T, temperature; R, resistance; RE, reference electrode; V, voltage; WE, working electrode. Part **a** adapted from ref. 20, Springer Nature Limited; adapted with permission from ref. 27, AAAS; adapted from ref. 29, CC BY 4.0 (https://creativecommons.org/licences/by/4.0/); reprinted from ref. 94, Springer Nature Limited; adapted with permission from ref. 96, Elsevier; adapted with permission from ref. 95, Elsevier; reprinted with permission from ref. 97, American Chemical Society; and adapted from ref. 98, Springer Nature Limited.

Wound exudate. Wounds disrupt the integrity of skin, and wound exudate can thus be sampled by on-skin patches or wound dressings[29,107]. However, biosensing of exudate cannot be applied for wounds with low exudate or for occlusive wounds. Exudate can be passively and directionally collected using liquid diodes that are regulated by the chemistry and topography of their microstructure, including wettability or curvature gradients and asymmetric structures[29,83]. Microfluidic channels for exudate delivery can also be patterned by engraving hydrophilic channels in omniphobic papers[108] or by embroidering hydrophilic threads on a hydrophobic woven fabric[109].

Interstitial fluid. ISF mainly exists between cells and is abundant at several hundred micrometres beneath the skin[110]. The dermis (~100 µm to 3 mm beneath the skin) has the highest ISF content and houses capillaries, making it the most suitable tissue for accessing ISF[111]. However, even the thickest regions of the dermis contain only ~120 µl cm^{-2} of available ISF[111]. Wick extraction, suction blisters, sonophoresis, microdialysis and thermal ablation can be applied to collect ISF, but these methods can cause local trauma or stratum corneum disruption[111,112]. Reverse iontophoresis is limited to collecting small molecules and the electrical current needs to be controlled to reduce irritation[113,114]. Microneedles with hollow, porous, solid or hydrogel-based swelling structures can also access or collect ISF and integrate sensors on the surface[115,116] or inside the hollow channel[117] and porous hydrogels[114] for in situ monitoring. In addition, hollow[118,119] or porous[120] microneedles with microchannels or porous hydrogel microneedles[121] can build pathways between the fluid-rich region and the sensing chamber (Fig. 4d). Such channels of needles can further contain pumps[119] for spontaneous and continuous sample collection and monitoring.

Saliva. Analytes in saliva can easily be accessed and directly sensed by a patch or mouthguard placed inside the mouth[122] or by wearable ring sensors through swab-based saliva collection[123]. Alternatively, saliva can be first collected using microchannels on the mouthguards with µPADs and then analysed by a colourimetric method[124] or first collected by pacifiers[97,125] and then analysed in a chamber isolated from the complex oral environment.

Tears. Analytes in tears can be assessed by sensors in the form of eye contact lenses with or without microfluidics. In particular, contact lenses with a microfluidic-based sensor can accumulate tears for the monitoring of multiple biochemical analytes[95,126,127] (Fig. 4d). The contact lens can also include a microfluidic chamber filled with liquid and a microfluidic channel filled with gas to sense intraocular pressure through variation of the liquid–gas interface in the sensing channel[128–130]. Furthermore, microchannels can help guide tears from the canthus to eyeglass-based sensors to minimize irritation[29].

Target recognition

Wearable flexible microfluidic sensors typically perform target detection through ion-selective recognition, direct redox reactions, catalyst-based reactions or bioaffinity recognition[8]. Ion-selective recognition allows electrolyte detection, for example, chloride and calcium ions, whereas direct oxidation is limited to detecting certain chemicals with characteristic redox peaks such as ferricyanide and pyocyanin. By contrast, catalyst-based and bioaffinity-based sensors can be used for a variety of metabolites (for example, lactate, urea and glucose) and biomarkers such as hormones (for example, cortisol, serotonin), cytokines (for example, IL-10, IL-1) and neurotransmitters (for example, dopamine)[131–133].

Catalyst-based recognition. In catalytic biosensors, catalysts, such as enzymes (for example, oxidoreductases, transferases, hydrolases, lyases, isomerases or ligases[134]), recognize analytes and generate

electroactive species or other detectable outcomes[135]. The sensing performance of catalytic biosensors can be affected by testing conditions such as pH, temperature, disturbance at sensing interfaces and the immobilization method, which can impact enzyme activity and the thickness and stability of the enzyme layer. Enzyme-based sensors have been designed for glucose, urea, lactate, alcohol and cholesterol detection[134]. However, the lack of sufficiently selective enzymes prevents their use for the detection of other biochemical analytes. In catalytic microfluidic biosensors, microfluidics are typically used to collect and convey biofluid to the sensing chamber[135].

Bioaffinity-based recognition. Affinity-based biosensors mainly include immunosensors, nucleic acid sensors, aptasensors and molecularly imprinted polymer (MIP) sensors; here, detection is based on direct and competitive binding or conformational transformation in response to the recognition of targets by receptors such as antibodies, single-stranded DNA, aptamers and MIPs[8,133]. Natural receptors of antibodies and single-stranded DNA can bind with high specificity to their respective antibodies and complements; by contrast, synthetic receptors, including aptamers and MIPs, can be designed to bind any type of target, enabling a variety of applications, including the detection of biomarkers related to disease diagnoses such as cortisol, dopamine and cytokines[133].

In flexible microfluidic affinity-based sensors, microfluidics cannot only collect, convey or propel biofluid but also contain reagents or detection antibodies with labels and introduce washing buffers to rinse unbound detection probes or labelling reagents[60,77,78,136]; for example, in a microfluidic immunosensor with a washing buffer chamber, a finger-press can initiate the delivery of washing buffer to the sensing chamber to rinse unbound analytes and wash out the sweat sample after incubation to achieve a low detection limit[78]. In sandwich mode lateral flow immunoassays, the sample pad and absorbent pad microfluidics collect sample and wick waste sample, respectively; the conjugate pad microfluidics is modified with a 'detector' antibody (usually labelled with coloured or fluorescent particles) and the analytical membrane microfluidics has an immobilized control reagent and 'capture' antibody to capture the analyte[137]. Following biofluid collection, the microfluidic system can drive the fluid with 'detector' antibodies and analytes conjugated to 'detector' antibodies to the detection area, where they generate a signal[21].

Continuous monitoring and sensor regeneration. Continuous and long-term biosensing is primarily based on catalysts, ion-selective membranes or direct redox reactions that do not involve irreversible binding of targets and receptors. For high-affinity sensors with slow dissociation kinetics, such as antibody-based and nucleic acid-based sensors with high sensitivity and selectivity, in situ regeneration and continuous monitoring remain challenging. Although most bioaffinity biosensors are applicable for one-time usage owing to the strong binding between bioreceptors and analytes, certain aptamer-based and MIP-based sensors that have fast dissociation kinetics for recognition events and limited sensitivity or a high limit of detection can operate continuously in situ[138–142]. To design flexible bioaffinity sensors for continuous monitoring with acceptable sensitivity and limit of detection, recognition with rapid dissociation kinetics[138], sensitive and amplifying transduction (for example, transistor-based approaches), or flexible microfluidics for efficient biofluid sampling can be included.

Recognition sites can be regenerated using chemicals (for example, acid–base buffers, detergents, glycine and chaotropes such as urea, dimethyl sulfoxide and ethanol[143]) or thermal or electrochemical techniques[10,133,144,145]. Owing to its convenience and ease of repeated control, electrochemical regeneration is especially suitable for wearable biosensors; for example, pre-programmed electrical stimuli, such as positive[146] or negative potentials[20] or electrical sweep potentials[147,148], can be applied to the sensor surface to introduce electrostatic repulsion[20] or redox reactions and trigger the unbinding of receptor-analyte complexes. However, regenerating the recognition sites without damaging bioreceptors or other components remains difficult.

Signal transduction

Optical and electrical techniques are typically used for signal transduction in wearable flexible sensors. Biochemical analytes (for example, electrolytes, metabolites, hormones, proteins) can be detected in biofluids by electrochemical and colourimetric techniques[29,61,101,102], and biophysical features (for example, sweat loss rate, ocular pressure, strain, temperature) can be sensed by electrical or optical sensors in biofluids or non-biofluids (for example, liquid metal or ionic liquid)[149,150].

Optical transduction. Optical sensors can detect physical and biochemical analytes by colourimetric, fluorescence and surface-enhanced Raman scattering (SERS) techniques (Fig. 4c,f); here, microreservoirs of flexible microfluidic sensing devices are typically prefilled with chemiluminescence reagents[27,151], fluorescent probes[56,152] or SERS chips[153,154] to recognize analytes through characteristic signals.

Colourimetric sensors, which benefit from low cost, ease of commercialization, simple fabrication, rapid visual readout and user-friendly operation, are commonly used to detect sweat loss rate[27,31,47], electrolytes (for example, chloride)[27,31,47], nutrients (for example, calcium, iron, zinc or vitamin C)[61], metabolites (for example, glucose, lactate and urea)[47,155] and physical analytes (for example, pH and temperature)[47]. In colourimetric sensors, the electron state change of chromophore molecules, stimulated by analytes or analyte-related chemicals, causes a shift in light absorption wavelength, which results in a colour change (for example, electrochromism, ionochromism and halochromism)[10]. Semi-quantitative and quantitative results can be acquired through naked-eye recognition or by using Red Green Blue analysis software. However, colourimetric sensing is only suitable for a narrow range of analytes and one-time use, with low selectivity and precision.

Fluorescence sensors rely on the selective reaction between fluorescent probes and targets, providing high sensitivity, high specificity and easy operation[156]; here, the target is detected by absorbing photons, which are then re-emitted at a longer wavelength.

SERS is based on Raman bands of the analyte that originate from vibrational and rotational modes specific to its molecular structure. These modes provide a chemical 'fingerprint', such as the chemical structure or crystallinity, for analyte identification[157]. SERS enables rapid, direct, non-invasive and label-free detection of biomarkers for the analysis of multiple molecules. However, both fluorometric and SERS techniques require portable light excitation modules and photodetectors. Thus, monitoring requires the operator to hold the spectrometer and scan continuously, limiting its portability and applicability[154].

Electrochemical transduction. Electrochemical sensors transduce biochemical recognition events into electrical signals such as potential, current, impedance or conductance. According to the detected signals

and electrode–biofluid interfaces, electrochemical transduction techniques can be divided into potentiometric, voltammetric, amperometric and impedimetric methods. Compared with colourimetric sensors, electrochemical sensors can sense multiple categories of compounds to generate a comprehensive biofluid profile.

Potentiometric sensing is mainly used for the detection of ions (for example, calcium, sodium, potassium and hydrogen ions) based on ion-selective membranes (for example, pH-responsive polyaniline)[18,158,159]. Voltammetric and amperometric techniques can detect redox-reactive molecules (for example, uric acid and vitamin C) based on the calculation of electrons transferred in and out of the working electrode[19,20]. Cyclic voltammetry, differential pulse voltammetry and square wave voltammetry can trigger reactions and record signals by applying changing voltages with controlled steps and speed to detect the corresponding currents[160,161]. Square wave voltammetry and differential pulse voltammetry can minimize interference from non-faradic current, resulting in high sensitivity.

Electrochemical sensors can be designed as labelled or label-free sensors (Fig. 4g,h). If recognition events do not result in characteristic electrical signals, external redox labels (for example, Prussian blue, methylene blue, ferrocene) can be tethered to the receptor to monitor recognition. However, such redox labels may deteriorate under long-term usage or harsh conditions (for example, high temperature, exposure to light), and they are susceptible to ionic species; for example, the electrochemical performance of Prussian blue can be affected by the concentration of ionic species in biofluids, and it degrades at neutral and alkaline pH; ferrocenium cations are sensitive to oxygen, resulting in chemical transformations in polar solvents during long-term usage[162]. Although methylene blue is more stable than Prussian blue and ferrocene, its monolayer can also degrade in response to changes in pH[163]. Alternatively, label-free sensors can be engineered using bio-field-effect transistor, electrochemical impedance spectroscopy (EIS), nanostructure catalysts or direct redox actions; for example, in EIS sensors, analyte binding events on the working electrodes can be captured by the variation of impedance, reflecting concentrations (for example, cortisol–aptamer[21] or peptide–antibody binding[88]). However, EIS sensors may have sensitivity problems owing to non-specific absorption on the electrode[59,164].

Other electrical transduction. Some physical analytes (for example, flow rate) can also be detected using mechano-electric, conductive and thermoelectric mechanisms (Fig. 4e); for example, strain and pressure can be sensed by encasing mechanoresponsive biofluids or non-biofluids in channels as the electrical properties (for example, resistance, capacitance, inductance) of fluids vary in response to mechanical stimulation of the channels[79]. Strain and pressure can also be detected using microchannels with an outlet and encased gas; here, the ratio of fluid and gas in the channel changes under different strains or pressures, which can be exploited as a pressure meter to indicate intraocular pressure[165]. Moreover, fluid volume and flow rate can be detected by monitoring fluid flow-induced channel-filling and the corresponding conductivity[56] and temperature variation[57] through electrical signals.

Microelectronics for wireless sensing systems

Wearable devices require wireless communication systems based on microelectronics. According to the digital communication protocols, wireless sensing systems can be categorized into near-field communication (NFC) and Bluetooth-embedded types. NFC-embedded systems[48,151,166] typically contain an external NFC reader (usually an NFC-enabled smartphone with NFC coils), an onboard antenna coil, an NFC system-on-chip with a built-in controller, analogue front-end and sensors. The NFC reader wirelessly provides power to and communicates with the onboard antenna that is connected to the system-on-chip and sensors, exploiting near-field magnetic resonance coupling at a frequency of 13.56 MHz with external coils, thus making the system battery-free. NFC modules can also be powered by sweat-activated cells for the monitoring of physiological information[167–170], albeit with limited powering and sensing capacity[31], preventing long-term continuous monitoring and multiplexed biochemical sensing. By contrast, Bluetooth-embedded systems, which typically consist of a microcontroller, analogue-to-digital converters, filters, integrated Bluetooth low energy[29] beacons and a battery, allow long-term continuous biochemical sensing. To reduce average power consumption, 'sleep' modes using power-gating and/or clock-gating circuit blocks can be designed to switch the microcontroller, analogue-to-digital converters and digital filters on or off[101].

Machine learning-driven and AI-driven biomedical sensing

Machine learning-based and artificial intelligence (AI)-based computations, based on the collected physiological condition data from individuals such as medical record, omics, imaging and diagnostics data, can be integrated into flexible microfluidic sensors to aid in medical decisions and construct the Internet-of-things in medicine[171]. Machine learning algorithms can interpret sensor readouts to identify and classify diseases for diagnosis and provide information on health conditions or disease progression for medical interventions[55,171]; for example, whole-body sweating may be predicted by measuring regional sweating rate and chloride concentration to aid in preventing dehydration[55]. Similarly, machine learning-enabled image processing algorithms may achieve automatic real-time image interpretation and analysis, alleviating the challenges associated with image variation, which typically requires expert intervention[171]. Flexible microfluidic sensors could also be integrated with such machine learning algorithms to discover drugs and apply precise treatment[172]. For example, AI can be used in precision medicine to tailor interventions for specific individuals or groups of patients, considering genomic variations as well as factors such as sex, age and family history[173].

Fluid-based biomedical sensing

Sweat sensors

Sweat contains ions (for example, sodium, chloride, potassium, calcium, hydrogen ions), metabolites (for example, lactate, ethanol, uric acid), nutrients (for example, amino acids, ascorbic acid), hormones (for example, cortisol), neurotransmitters (for example, neuropeptide Y, dopamine, serotonin) and proteins (for example, cytokines)[8,53,59]. Therefore, sweat can be collected for non-invasive health and drug monitoring[59,174]; for example, the concentration of sodium and chloride in sweat can reflect electrolyte loss and hydration state during exercise; the concentration of ammonium ions in sweat can be related to liver and kidney function as well as exercise intensity[8]; sweat glucose levels can be related to blood glucose for diabetes diagnosis[175]; sweat neuropeptide Y and cortisol levels show good correlation with those in blood[8,28,78].

Most wearable microfluidic sweat sensors have been designed to analyse sweat during exercise by monitoring sweat rate[27,48,55], potassium, sodium, chloride, glucose and lactate levels[102,176]. Ions and metabolites are typically present in the millimolar or micromolar range in sweat, which allows their detection by ion-selective and enzymatic

electrodes or by colourimetric reagents. By contrast, amino acids, vitamins and lipids, which also play important roles in nutrition or metabolic diseases (for example, diabetes and metabolic syndrome)[61], are typically found in micromolar levels in sweat and cannot yet be continuously monitored. Of note, a MIP-based flexible microfluidic biosensor integrated with iontophoresis-based sweat stimulation and constant potential-repelling-induced recognition site regeneration can continuously monitor multiple amino acids and metabolites[20]. The concentration of hormones, neurotransmitters and proteins in sweat is typically in the range of nanomoles and picomoles[59,177], and these are therefore difficult to detect. Cortisol can be measured in sweat using a flexible wearable microfluidic field-effect transistor-based biosensor with signal-amplifying ability[28], a microfluidic-based immunosensor integrated with EIS[77,136] or a colourimetric microfluidic immunoassay[21]. Picomolar levels of neuropeptide Y can be measured by a label-free flexible microfluidic immunosensor that integrates EIS[78]. This sensor achieves a low detection limit of 50 fM owing to microfluidic-based rinsing of unbound target on the sensing electrode surface[78].

Wearable sweat sensors may also be applied to monitor proteins in inflammatory diseases[178] and to measure the concentration of drugs such as caffeine[103], levodopa[179], paracetamol[180], paroxetin[180] and ethinylestradiol[180]. However, monitoring drugs, in particular, macromolecules at low concentrations in sweat, remains challenging.

ISF sensors

ISF is located between cells underneath the skin and formed during a transcapillary exchange between cells, blood and lymphatic capillaries. Thus, ISF contains similar metabolomic and proteomic profiles as blood[111,181,182] but does not clot. Therefore, ISF can be assessed to continuously monitor various biomarkers and therapeutic drugs for disease management[182], particularly small molecules with a molecular weight of less than 3 kDa (for example, ions, glucose, urea, vancomycin and cortisol), which paracellularly diffuse from blood to the ISF, showing almost equal concentrations in both fluids[111]. Wearable flexible glucose sensors based on reverse iontophoresis can collect and analyse ISF[58]. Similarly, microneedles with[119] or without microfluidics[101,120] can monitor antibiotics (for example, vancomycin and tobramycin)[142], anticancer drugs (for example, doxorubicin)[139], anticoagulant and procoagulant drugs (for example, thrombin)[142] and drugs for the treatment of Parkinson disease (for example, levodopa)[183].

Biomarkers with a molecular size of more than 3 kDa (for example, insulin, haemoglobin, cytokines, albumin and antibodies) do not diffuse from blood to the ISF and thus have only low concentrations in ISF[111]. Therefore, a diagnostically meaningful correlation between ISF and blood concentrations of these biomarkers has yet to be verified; however, ISF can also be analysed to confirm the existence of an analyte. Moreover, some cytokines can be detected earlier in dermal ISF than in blood and at higher concentrations than in serum[111]. Thus, the ISF may be analysed to monitor the immune system in the treatment of infections (for example, influenza)[184] and inflammatory disorders (for example, lupus)[185]. For example, *Plasmodium falciparum* histidine-rich protein 2 can be detected in ISF for the diagnosis of malaria infection using a hollow microneedle-integrated colourimetric μPad[118].

Integrating flexible microfluidics into microneedles enables the collection of ISF; however, it remains unclear whether the extruded ISF can provide useful diagnostic information for long-term monitoring because microfluidic-based ISF extraction may disrupt the balance of pressure between ISF, blood, and lymph and trigger local inflammation, which may alter the concentrations of analytes in ISF[111].

Wound exudate sensor

Wound exudate is derived from a variety of endogenous (for example, bloodstream, local and migrated cells) and exogenous sources (for example, bacteria) through extravasation, inflammatory and infection processes[186]. Wound exudate typically contains electrolytes, metabolites (for example, glucose and uric acid), proteins (for example, cytokines, lysozyme and matrix metalloproteinases (MMPs)), cells (for example, leucocytes and macrophages) and microorganisms[187,188]. The composition of wound exudate varies according to wound types and healing stages, impacting wound status monitoring and wound management. For example, a pH of ~4–6 and active growth factors can be found in acute healing wounds, whereas a pH of ~7–9 and proteolytic enzymes can be seen in a chronic wound, which can be measured to monitor wound healing status[187,188]. High uric acid levels can be related to wound severity and excessive reactive oxygen species[189]. Wound exudate glucose levels correlate with blood glucose levels and bacterial activities[190]. Microorganisms and virulence factors can be assessed for infection monitoring[29,191]. High levels of MMPs, in particular, MMP2, may be related to wound exacerbation[192]; similarly, MMP levels can be assessed to monitor the therapeutic effect of MMP inhibitors in wound healing[193].

Wound infection can be monitored by wireless wearable bioelectronic sensors that can measure pH and detect small molecules, including ammonia, glucose, lactate and uric acid[107,190,194]. However, owing to the abundance of macromolecules in wound exudate, including proteins, enzymes and virulent factors, wearable sensing of specific analytes remains challenging owing to irreversible affinity, limited longevity and matrix interferences. A multiplexed microfluidic affinity-based biosensor can monitor inflammatory biomarkers (tumour necrosis factor (TNF), IL-6 and IL-8) and healing status biomarkers, including transforming growth factor-β1 (TGFβ1), *Staphylococcus aureus*, temperature and pH[29], albeit not yet over long periods. Moreover, polymer-based and fibre-based wireless wearable microfluidic wound sensors may be integrated with dressings or bandages[29,107–109]; however, fibrous wound sensors that are gas permeable and easily integrated with dressings or bandages are not yet compatible with large-scale manufacturing techniques such as roll-to-roll processing, laser cutting and printing.

Saliva sensors

Saliva is a complex mixture of chemicals secreted from salivary, parotid, submandibular and sublingual glands, reflux of gastric juice, mucosal transudate, gingival crevicular fluid, microorganisms, epithelial cells, and food debris[195,196]. Saliva is composed of ~98.5% water and ~1.5% biochemicals, including ions, metabolites, enzymes (for example, amylase, lingual lipase lysozyme, peroxidase and lipase), hormones (for example, cortisol), proteins (for example, mucin and cytokines) and microorganisms[197]. A healthy adult typically generates ~0.5–1.5 l of saliva per day, with a flow rate of 0.1, ~0.3–0.4 and ~4–5 ml min^{-1} during sleep, at basal levels, and during eating or chewing, respectively[198]. The saliva composition is influenced by diet, disease, drugs and physiological states such as fatigue and stress[199]. Therefore, saliva composition can give insight into the health status and can be analysed for drug and diet management[200,201].

Wearable flexible saliva sensors have been designed to monitor oral diseases (for example, volatile sulfur compounds for dental caries)[196], metabolic diseases (for example, glucose for diabetes or uric acid for hyperuricaemia) and microorganism infection[196,201], and to track food or drug intake (for example, salt, alcohol and

tetrahydrocannabinol)[196,202]. Flexible microfluidics can be integrated with wearable flexible saliva sensors to improve sensing; for example, smart and soft microfluidic pacifiers can be applied in neonatal intensive care units[97,125] to continuously collect saliva; here, saliva is transported through a channel to the sensing chamber, which is located outside the mouth. However, owing to the low concentration of certain analytes in saliva, its complex chemical matrix and harsh physical surroundings, the impact of food intake, and the current lack of suitable sensing methods, only a few wearable saliva sensors have been explored for disease monitoring; for example, wearable sensors have been designed to detect interleukins and cytokines in saliva to diagnose periodontitis, oral squamous cell carcinoma and gastric cancer[200].

Tear sensors

Tears are primarily secreted by the lachrymal glands and goblet cells at a rate of ~1–3 µl min^{-1}, forming a tear film on the ocular surface with a volume of ~2.73–12.75 µl (ref. 203). The tear film contains 98% water and 2% other components, including proteins, lipids, glucose and lactate[204]. Tears can be categorized into basal, reflex, and physico-emotional tears, each with a different composition[205]. Owing to the blood–ocular barrier, the biochemical components of tears differ from those of blood[206,207]. However, the barrier can be disrupted by intraocular inflammation, vascular disorders, systematic disorders, intraocular tumours and other factors, leading to an increase in inflammatory cells, cytokines, proteins and growth factors in tears[207]. Thus, tears can provide information related to ocular or systematic diseases; for example, a high concentration of inflammatory cytokines, such as IL-1, IL-6 and TNF, may be associated with dry eye disease, ocular allergy[208] and neural disorders (for example, Parkinson disease[209]). In addition, the glucose concentration in tears correlates with blood glucose levels in patients with type 1 and type 2 diabetes[207]. Moreover, neural transmitters, such as dopamine and catecholamines, can be detected in tears and are related to the progression of glaucoma[207].

Flexible microfluidic-based contact lens sensors can collect and analyse low volumes of tears using optical transduction methods[206,210]; for example, fluorescence and colourimetric microfluidic contact lens sensors can monitor pH, ions (for example, sodium, potassium, calcium, magnesium and zinc), glucose, proteins and nitrites in tears[95,126]. However, direct contact of tears with non-biocompatible materials or rigid electronics in electrochemical sensing systems can cause discomfort and irritation, which can be prevented by embedding miniaturized electrochemical sensors and rigid microelectronics in contact lens hydrogels to minimize irritation and achieve wireless monitoring of glucose[211,212] and cortisol[213]. Such systems also allow closed-loop drug delivery into tears[210,214]. However, the integration of flexible microfluidics with electrochemical contact lens sensors remains challenging owing to the strict requirements of miniaturization, biocompatibility, comfortability and transparency. Alternatively, a microfluidic electrochemical sensor can be fabricated as an eyeglass accessory; for example, a flexible microfluidic electrochemical sensor can be implemented on eyeglasses by mounting a microchannel onto the nose bridge to reach the eye socket and measure glucose, alcohol, and vitamin B2, C and B6 concentrations[96].

Non-biofluid sensors

Microfluidic devices are typically used as tools to collect, transfer and store liquid samples in biomedical sensors; however, their confined channel configurations and the softness of PDMS also make them excellent sensing components. By filling microfluidic channels with a conductive liquid, such as Galinstane, eutectic gallium indium alloy[215] or ionic liquids[216], the channels can serve as passive circuit components such as conductors, resistors, capacitors and inductors. For example, a device with Galinstane-filled and ionic liquid-filled channels, which act as electrodes and dielectrics, respectively, can capacitively sense temperature, humidity and oxygen levels[149]. By designing more complex microchannels, such as serpentine and spiral channels, physiological parameters, such as heart rate and tactile information from human fingers, can be measured based on strain sensing[217] (Fig. 4i). Similarly, liquid metal confined in an elastomer microtube enables strain sensing, which can be integrated into textiles for pulse monitoring[79]. In addition to conductive materials, non-conductive flowing liquid and gas-filled channels can be implemented in an intraocular lens to monitor intraocular pressure for the diagnosis of glaucoma[129]. Similar designs have been used for contact lenses integrating eye pressure sensors[130,206] and intra-abdominal pressure sensors[218].

Challenges and outlook

Wearable flexible microfluidic-based sensors have the potential to transform disease diagnosis and health management by enabling decentralized point-of-care disease detection, diagnosis and monitoring. However, only a few prototypes and products have yet reached the market (Box 2), and various challenges remain to be addressed.

Wearable microfluidic devices have to provide clinically useful, reproducible and reliable information, which needs to be validated by gold-standard diagnostic methods and results obtained from blood samples. The impact of the measurement environment on reliability, including effects of chemical influences (pH, biofouling or other biochemicals in biofluid matrix), physical interferences (for example, abundant motions or temperature) and collection (for example, immune reaction under long-term extraction and extraction of large volumes or the use of stimulants), needs to be thoroughly investigated for each device. In particular, long-term usage or continuous monitoring, which are highly desired for chronic disease management and pre-disease diagnostics, need to be optimized; for example, in electrochemical biosensors, particularly affinity-based electrochemical sensors, binding between targets and receptors is typically irreversible, and the recognition sites are difficult to regenerate. Moreover, changes in the physical and biochemical environment, such as strain, biofouling and temperature, can induce microcracks, dysfunction and alteration of functional layers, resulting in the deterioration of electrochemical sensors. Similarly, redox labels and mediators gradually degrade during long-term usage. Additionally, the soft–rigid interfaces between tissue and electronics or among different components may deteriorate, causing unreliable data collection or transmission. Furthermore, flexible microfluidics may become dysfunctional owing to leakage, blockage or deformation. Therefore, materials and engineering strategies need to be developed to achieve reversible recognition, seamless systematic integration and robust sensors with stable sensitivity, selectivity and stability. For example, stable redox labels could be developed that can withstand light, pH and temperature variations. Label-free sensing methods could be designed with high sensitivity and signal amplification by exploring artificial catalysts with high selectivity for redox reactions. In addition, receptors could be designed that can continuously and rapidly recognize specific analytes with efficient bind-dissociation kinetics. Finally, automated techniques are required for the regeneration of recognition sites.

Box 2

Translational considerations

The translation of flexible microfluidic devices requires confirmation of the detection of accurate and reliable information about the tested physiological parameters or pathological conditions, which should be comparable to clinically applied diagnostic tests. Therefore, the sensor needs to ensure selectivity, sensitivity, low detection limit, minimum interference and minimal false readout. In addition, the sensor should be stable and tolerate the various conditions of daily usage such as repeated physical motion, wet conditions and complex microenvironments (pH, biofouling and other biochemicals).

User experience is also crucial for commercialization. Ideally, the device is designed as a miniaturized, comfortable, easy-to-operate and low-cost wearable system with few or no calibration steps or irritation to the skin. In addition, wireless communication to other devices should be integrated and a long-lasting battery life ensured.

Examples of commercialized wearable microfluidic devices include the Discovery patch from Epicore Biosystems for sweat collection, which has been approved by the FDA; Gx Sweat Patch from Epicore Biosystems (colourimetric readouts for sweat rate and sodium concentration)[230]; Nix hydration biosensor (electrochemical signals for sweat loss configuration and composition)[231]; My Skin Track pH, cooperatively developed by L'Oréal and Epicore (colourimetric sweat pH measurement)[232]; Connected Hydration by Epicore Biosystems (continuous measurement of sweat volume, electrolyte loss, and body temperature and movement)[233]; smart insole from FlexoSense (using liquid metal-based microfluidic sensors that map foot pressure distribution for patients with diabetes to monitor and manage foot diabetic ulcers or to prevent re-ulcerations)[234]; and ARIS muscle analyser from Microtube Technologies (liquid metal-based microfibre sensors that track muscle movement and repetitions in stationary workouts and, at the same time, provide workout analysis and recommendations).

The large-scale fabrication of scalable, simple, cheap and stable disposable wearable microfluidic devices intended for one-time use (for example, for the detection of infection events) also remains challenging. Although printing, scalable laser cutting and roll-to-roll techniques can be applied for their large-scale production, these methods do not allow the design of multiplexed electrochemical biosensors with complex components and reusable microelectronics. Therefore, engineering techniques need to be established for the large-scale production of low-cost biosensors, in particular for the formation of films of even, functional layers on microneedle sensors and sensors with 3D structures.

Integrating wearable microfluidic fluorescence and SERS sensors with a wearable spectrometry system faces the challenge that the spectrometry system is typically bulky and can thus not be easily integrated with wearable devices. Alternatively, miniaturized spectrometry systems would allow integration into a printed circuit board in the form of a watch or band.

Most wearable microfluidic sensors are currently limited to a few metabolites and electrolytes. Wearable sensors that can detect hormones, proteins and peptides with a molecular weight of more than 3 kDa (for example, neuropeptide Y and cytokines) are more challenging to design owing to their low concentration in body fluids, including in sweat, tears, ISF, wound exudate and saliva, as well as an unclear correlation with their concentrations in blood. To realize their reliable detection, signal-amplifying methods and efficient recognition approaches (such as aptamer–antibody recognition with a dissociation constant in the nanomole range) would be required.

Next-generation disease management may greatly benefit from multiplexed wearable microfluidic sensors that can incorporate AI or data mining, the Internet-of-things and drug delivery modules with feedback loops. Such systems could also be designed to be integrated with conformable printed circuit boards, microelectronics and self-powered, sustainable, flexible power supplies. Interdisciplinary efforts, involving engineers, scientists and clinicians, will thus be required to translate effective and accurate sensors to the clinic to improve disease prediction, diagnosis and monitoring as well as personalized health management.

Citation diversity statement

We acknowledge that papers authored by scholars from historically excluded groups are systematically under-cited. Here, we have made every attempt to reference relevant papers in a manner that is equitable in terms of racial, ethnic, gender and geographical representation.

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Author contributions
C.T.L., J.Y.L. and S.W.C. discussed and conceived the idea for the synopsis. C.T.L. and S.W.C. guided all aspects of the work. C.T.L., J.C.Y. and J.Y.L. refined the manuscript. S.W.C., Z.Q. and Y.N. drew most figures and wrote and finalized the content. J.C.Y., J.Y.L., Y.C.L., X.Y.L., S.C.F. and J.M.Q. contributed to writing the first draft. All authors contributed to discussing, editing and finalizing the article.

Competing interests
C.T.L. is an inventor on patents related to a smart insole from FlexoSense and an ARIS muscle analyser from Microtube Technologies. These patents have been licensed to FlexoSense and Microtube Technologies, respectively. C.T.L. is a scientific founder of the above two companies and holds equity in them. The remaining authors declare no competing interests.

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