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## Recent advances in skin-like wearable sensors: sensor design, health monitoring, and intelligent auxiliary

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When entering old age, the tissue structure of the body begins to age, the functions of various organs appear disordered, resistance declines and is prone to various geriatric diseases. Geriatric diseases are characterized by a long course of the disease, slow recovery, and high medical costs. Therefore, a simple, rapid, economical, and effective method is urgently needed to detect the indicators of patients for long-term and continuous monitoring to reduce the medical burden. Wearable sensors, with their advantages of real-time, economical, simple operation, and non-invasion have attracted extensive attention and have good application potential in the health monitoring of elderly patients and the development of intelligent auxiliary devices. This paper reviews the research progress of skin-like wearable sensors in health monitoring and intelligent auxiliary devices in recent years. According to different sensing mechanisms, this paper introduces skin-like wearable sensors for health monitoring, including electrochemistry, bioimpedance, photoelectricity, and other wearable sensors, as well as related research for the development of intelligent auxiliary devices. Finally, this paper summarizes the applications and future challenges of developing the skin-like wearable sensor into a widely used and accepted home medical device for elderly patients.

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### 1. Introduction

Geriatric diseases refer to a class of aging-related diseases from which people in old age are prone to suffer with its own characteristics.<sup>1,2</sup> As the human body enters the old age, tissues begin to age, and the function of various organs is impaired, while the resistance gradually weakens, the adaptability declines, and it is susceptible to various senile diseases, such as coronary heart disease, bronchitis, diabetes, and Parkinson's disease.<sup>3,4</sup> The etiology of these diseases is often not so clear that there are no obvious symptoms and signs in the early stage, and the disease changes in various ways, with

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a lack of specific treatment. In addition, geriatric diseases have a long course of the disease and slow recovery. Patients in the late stage of the disease often suffer from several geriatric diseases at the same time. Long-term clinical treatment leads to excessive medical burden and poor quality of life for patients. The excessive medical burden may lead to negative treatment of patients, resulting in further deterioration of the elderly, increasing medical costs, and falling into a vicious circle.<sup>5</sup> Therefore, there is an urgent need for a simple, rapid, economical, and effective method to monitor patient indicators for a long time and continuously, so as to reduce the medical burden of patients and improve their quality of life.

At present, the traditional health monitoring methods mainly rely on traditional technologies, such as intravenous catheterization and large-scale ECG monitors, which require the use of cumbersome instruments and complex operating procedures, and have drawbacks such as time consuming, high cost, complex operation, and easy pollution, so they are not suitable for long-term real-time monitoring of the body state.<sup>6,7</sup> In addition, samples may be obtained in a way that is invasive and may cause discomfort and pain to patients.<sup>8,9</sup> In order to achieve the efficiency and acceptable degree of health monitoring, wearable sensors have been widely studied due to their advantages of real-time and long-term monitoring, non-invasive reliability, simplicity, and rapidity.<sup>10</sup> Most importantly, wearable sensors have been widely used in health monitoring and in the development of intelligent auxiliary devices.

Global attention to health problems such as obesity has gradually radiated from the pharmaceutical industry to all walks of life, such as software and hardware. At the same time, with the aging of the population and the prevalence of cardiovascular disease, there is an increasing need to develop individual health care systems, thereby enabling early disease detection and timely response.<sup>11</sup> The use of wearable technologies, which are becoming more prevalent among the general public, combined with smartphones and health apps that can record and monitor vital signs such as calorie expenditure, fitness activities, pulse, body weight, heart rate, oxygen levels, and sleep patterns without the restrictions of time and place,<sup>12,13</sup> will initiate a revolution in health care systems.<sup>14</sup> The wearable devices are not affected by the age of the users. They are convenient, non-invasive, and suitable for the elderly. It has a great impact on the growing old population. The new wave of body sensor devices is likely to have a significant impact on health care systems and quality of life. Wearable fitness sensors are popular worldwide and continue to grow in annual sales.<sup>15,16</sup>

Skin-like wearable sensors with a single function or multi-function play an important role in medical care, the development of smart devices, and other fields.<sup>17–21</sup> This kind of wearable sensor can be attached to human skin and clothing surfaces, which has strong scalability, flexibility, and adhesion-ability.<sup>22–24</sup> It can be designed as health monitoring devices for real-time monitoring of the user's respiratory rate, exercise frequency, body temperature, blood pressure, pulse,

*etc.*, within a certain period of time, and for long-term health monitoring of the body state. In addition, due to their excellent performances, the skin-like wearable sensors can be designed as intelligent auxiliary devices to help users complete necessary daily activities.<sup>25</sup> In addition, the skin-like wearable sensor is simple in shape, small in size, and light in weight, which will not cause other burdens to users. For elderly patients with a long disease course and heavy treatment burden, home remote monitoring is helpful to help patients monitor body signals at home and reduce medical costs. The skin-like wearable sensors can be highly attached to the human skin or the surface of clothing with high comfort and acceptability. It has good application potential in health monitoring of elderly patients and assisting elderly patients in their daily life. Recent advances in health monitoring devices and intelligent assistive devices based on skin sensors can be seen in Fig. 1.

In this review, according to different sensing mechanisms, we reviewed a variety of skin-like wearable sensors, including electrochemical, bioimpedance, photoelectric and other wearable sensors and the research progress on the health monitoring and the development of smart assistive devices in recent years. Finally, we summarized the applications and future challenges of developing the skin-like wearable sensor into a widely used and accepted home medical device for elderly patients.

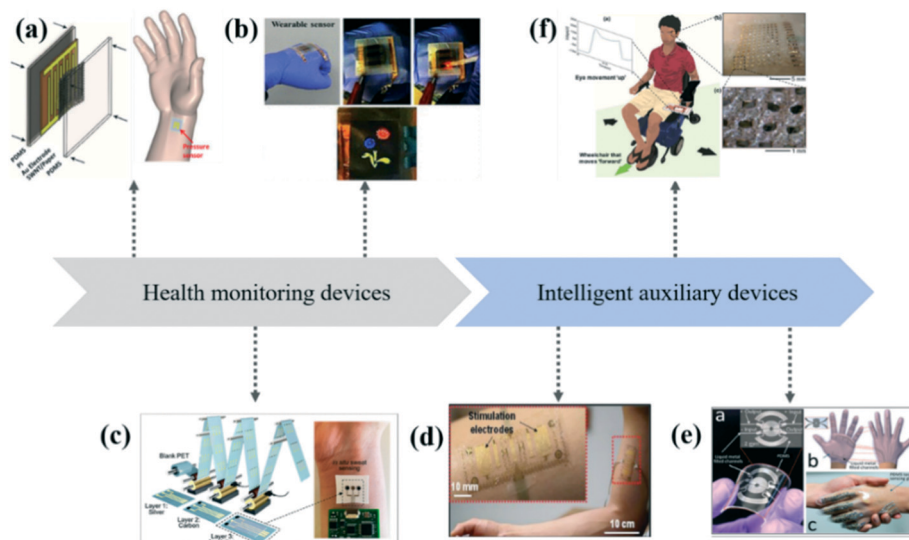
## 2. Design of skin-like wearable sensors

The basic components of wearable sensors are:<sup>26</sup> 1. The flexible substrates used to support other materials such as sensing components and conversion devices usually selected with stretchable and flexible poly-dimethylsiloxane (PDMS) and Ecoflex;<sup>27</sup> 2. The affinity of wearable sensors is usually improved by modification with biorecognition elements.<sup>28</sup> Immobilized biological and sensitive materials used as recognition elements, including enzymes, antibodies, aptamers, and other bioactive substances;<sup>29</sup> 3. The sensitivity of wearable sensors can then be enhanced by the addition of nanomaterials to achieve signal amplification.<sup>28</sup> The commonly used nanomaterials in wearable electrochemical biosensors and their characteristics are as follows:

1) Carbon based nanomaterials, such as graphene oxide (GO), reduced graphene oxide (rGO), and carbon nanotubes (CNTs), have the major advantage of increasing the electron transfer rate. In addition, the electrical conductivity and surface area can also be improved by chemically functionalizing the surface structure, leading to improved sensitivity of wearable sensors.<sup>30,31</sup>

2) Metallic nanomaterials such as gold nanoparticles (AuNPs), palladium nanoparticles (PdNPs), platinum NPs (PtNPs) and bimetallic composites: Au–PtNPs. Due to the strain and electronic effects of bimetal, bimetal nanomaterials show excellent performance and can be used as stabilizers for biometric components while promoting good electron transfer between target materials and sensing interfaces. The surface of





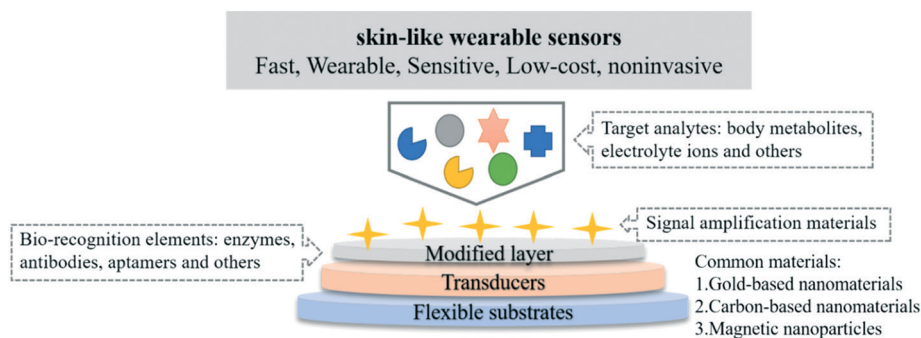
**Fig. 1** Recent advances in health monitoring devices and intelligent assistive devices based on skin sensors. (a) A flexible, wearable, and flexible skin-like pressure sensor, which could monitor important physiological signals in real time.<sup>97</sup> (b) A wearable tactile sensor that responds instantly to external stimuli.<sup>159</sup> (c) A wearable sensor based on the roll-to-roll (R2R) gravure printed electrodes for real-time, *in situ* perspiration monitoring during exercise.<sup>160</sup> (d) An irritable, skin-like wearable sensor can induce muscle contractions by increasing electrical levels to aid in the recovery of paralyzed limbs.<sup>157</sup> (e) A smart prosthesis based on skin-like sensors can be used by patients to receive tactile sensations as they grab, grab, squeeze, shake or touch.<sup>161</sup> (f) A soft, conformal bioelectronics for a wireless human-wheelchair interface.<sup>162</sup>

Au–PtNPs with large pores can significantly improve the specific surface area and electrocatalytic performance of the electrodes.<sup>32</sup> Amine or thiol linkers and various functional groups (–SH, –NH<sub>2</sub>, –CN) can assist gold nanoparticles in forming multilayer composite films at the sensor interface.<sup>33</sup>

3) Magnetic nanoparticles (MNPs), generally composed of a magnetic inner core composed of metal oxides such as iron, cobalt, and nickel and a polymer/silicon/hydroxyapatite shell wrapped outside the magnetic inner core, are a new class of materials that have been developed rapidly and are of great application potential in recent years.<sup>34,35</sup> As both magnetic and polymeric particles, magnetic nanoparticles have the characteristics of magnetic guidance, biocompatibility, small size effect, surface effect, active groups, and certain biomedical functions. The surface modification of MNPs can not only enhance the stability of magnetic nanoparticles, but also improve their dispersion and biocompatibility in aqueous solution, improve

targeting, prevent protein adsorption, increase their time in blood circulation, and further compound other nanoparticles, compounds, or biological ligands to realize the functionalization of magnetic nanoparticles.<sup>36,37</sup> Moreover, MNPs can be controlled by an external magnet, which enables reproducible magnetic virus separation and further signal amplification in real clinical samples when simultaneously attaching target materials and biorecognition elements.<sup>38</sup> The components of skin-like wearable sensors are displayed in Fig. 2.

The wearable sensors can use different sensing mechanisms to detect target signals, and the selection of sensing mechanisms is determined by the design of the sensor, the materials used, and the target signals. The following will introduce the design of wearable sensors from different types of sensing mechanisms. The recently reported performance reviews of wearable sensors based on different sensing mechanisms are shown in Table 1.



**Fig. 2** Schematic description of components for skin-like wearable sensors.



## 2.1 Electrochemical wearable sensors

The electrochemical sensing mechanism is to measure the concentration of the target object according to the change of current, potential, impedance, or other electrical parameters when the target analysis is present.<sup>46,47</sup> Electrochemical sensors have great potential in the development of wearable devices because of the advantages such as miniaturization, low budget, and simple operation. Electrochemical wearable sensors can noninvasively monitor the concentration of target biomarkers in different body fluids (such as sweat, urine, saliva, *etc.*) to analyze the health status of users.<sup>48</sup>

Anastasova *et al.*<sup>49</sup> designed a fully integrated flexible skin-like microfluidic platform (Fig. 3) that simultaneously detected metabolite concentrations (lactic acid, *etc.*), electrolyte levels (pH, sodium, *etc.*) in human sweat, and autonomously calibrated internal temperatures. 1. By using polyvinyl chloride (PVC) functional film, a potential type sodium ion sensor was constructed on the inner layer of electrochemically deposited poly(3,4-ethylenedioxythiophene) (PEDOT) polymer. 2. A pH sensor was constructed based on iridium oxide film (IrOx) with high sensitivity. 3. Ampere-type lactic acid sensor was composed of doping enzymes deposited on the semi-permeable copolymer film and the outer polyurethane layer. The volunteers wore the prepared skin-like sensor patch for cyclic experiments, and the changes in pH measurements, sodium, and lactate concentration measured are shown in Fig. 3. This method had been successfully applied to monitor multiple targets simultaneously, demonstrating the potential of an integrated skin-like wearable platform for the long term, thereby using for monitoring target analytes in body fluids consistently, which could be used to monitor the health status.

## 2.2 Optical wearable sensors

Optical sensors have been successfully applied in various applications,<sup>50,51</sup> for example, including in a wrist smart watch (for heart rate detection) and a pulsed blood oxygen wearable sensor. In the environment, light enters the body through the skin. Based on the changes in optical properties (*e.g.*, absorption and scattering), the detector can capture changes in body data. The wavelength can extend from infrared to ultra-

violet, depending on the penetration depth requirements of each detection application.<sup>52</sup> Flexibility and stretchability of the wearable device affect the accuracy of the signal and adhesion to the skin.<sup>53</sup>

Among them, wearable sensors based on optical fiber have attracted more and more attention because of their advantages of good anti-interference, high sensitivity, small size, and ease in implementing multiplexed or distributed sensors.<sup>54,55</sup> In recent years, people have vigorously promoted the development of optical fiber sensors, sensing technology for high sensitivity optical imaging of high resolution and other excellent performance is also gradually increasing in demand. As a combination of fiber optics and nanotechnology, optical micro/nano fibers (MNF) with smooth surface, good mechanical flexibility, micro/nano structure, and other properties have become a good choice for improving sensor sensitivity, response speed, optical resolution, and detection performance.<sup>56,57</sup> The basic structure, functional materials, and signal conduction used by the MNF sensor are shown in Fig. 4. The sensing mechanism of the MNF sensor is complex. Next, the sensing mechanism of the pressure MNF sensor will be introduced through an example. For example, Tang *et al.*<sup>58</sup> proposed a compact tactile sensor (CTS) with a diameter of 1.5 mm based on optical MNF materials, which could convert tactile and pressure stimuli into observable and comparable optical signals. As shown in Fig. 5a, the PDMS and Teflon tubing encapsulated a U-shaped MNF that had been attached to a silica capillary, and a micro-dome would be observed at the tip of the Teflon tubing. When the sensor contacts the object and is subjected to pressure stimulation, the crook degree of MNF will increase with the increase of pressure stimulation, resulting in the reduction of the output intensity transmitted by MNF (Fig. 5b). Thus, qualitative and quantitative analysis of the contact object and pressure stimulus is carried out through the output light intensity. The performance of the sensor is tunable in a wide range by changing the MNF diameter or the gap between the MNF and the apex of the micro-dome (Fig. 5c–e). This sensor could instantly sense the contact of objects and pressure stimuli, and the pressure detection sensitivity was up to 0.108 mN<sup>-1</sup>, and the resolution was 0.031 mN. This sensor provides some ideas for developing artificial intelligence products of object recognition.

**Table 1** Summary of the performance of wearable sensors based on different sensing mechanisms reported recently

Sensing materials	Mechanism	Linear range	Sensitivity	Response time	LOD	Ref.
Au/PtNP onto ACF	Electrochemical	Glucose 0–1000 μM	22.8 ± 0.7 μA mM <sup>-1</sup> cm <sup>-2</sup>	—	1.7 ± 0.7 μM	39
		Choline 0–350 μM	9.4 ± 3.9 μA mM <sup>-1</sup> cm <sup>-2</sup>		10.5 ± 3.7 μM	
		Lactate 0–20 mM	4.1 ± 0.3 μA mM <sup>-1</sup> cm <sup>-2</sup>		4.6 ± 3.0 μM	
Transdermal graphite/Teflon/AOx/HRP	Electrochemical	Ethanol 0.01–13.0 mM	0.07 ± 0.003 μA mM <sup>-1</sup>	—	—	40
AOx/Pt on poly( <i>o</i> -phenylenediamine) film	Electrochemical	Alcohol 5.0 ± 80.0 mM	0.045 nA mM <sup>-1</sup>	—	—	41
MKR (microfiber)/gold on PDMS	Bioelectrical impedance	—	0.83 kPa <sup>-1</sup>	20 ms	30 Pa	42
Monolayer graphene on PDMS	Piezoresistive	Pressure 0–12 kPa	8.5 kPa <sup>-1</sup>	40 ms	1 Pa	43
CuTCNQ nanowire arrays on PI film	Piezoresistive	Pressure 0–1500 pa	6.25 kPa <sup>-1</sup>	10 ms	0.73 Pa	44
VHB/AgNPs on PDMS	Resistive	Pressure 1.5–6.5 kPa	0.48 kPa <sup>-1</sup>	250 ms	—	45



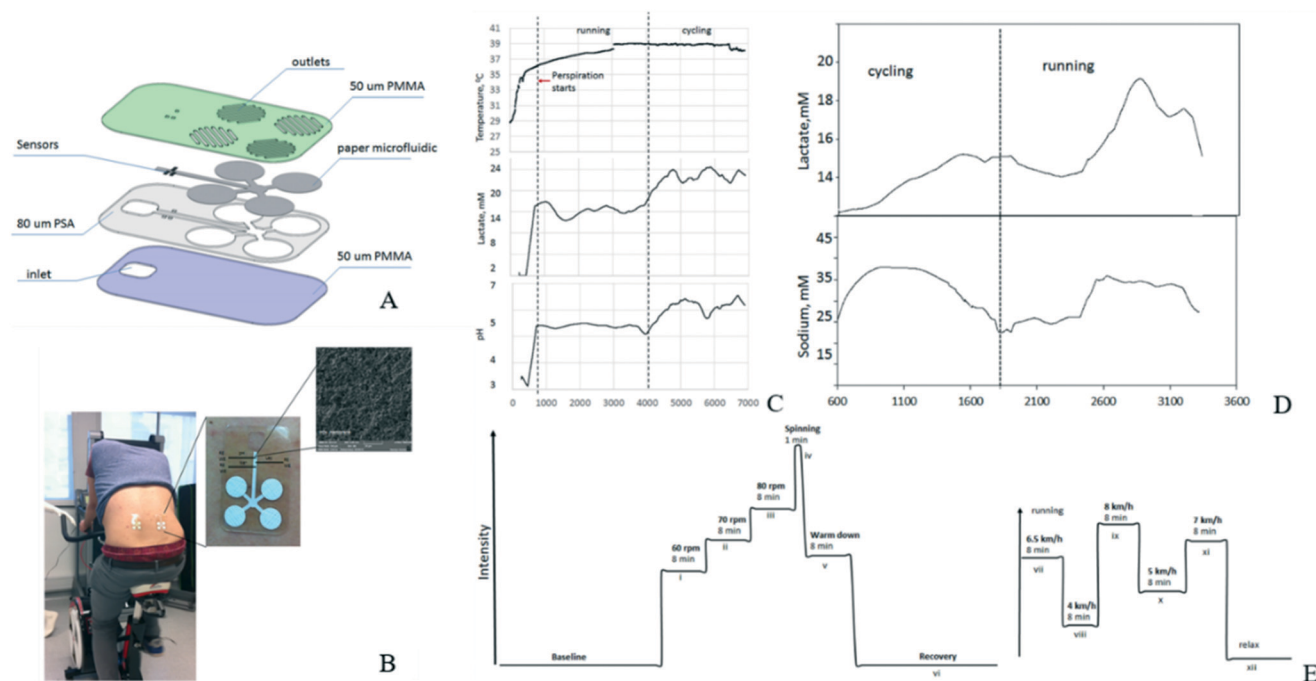


Fig. 3 (A) Schematic representation of the fabrication steps of the micro-fluidic chip; (B) photo of the platform attached to the body and scanning electron microscopy (SEM) image photo of IrOx pH sensor membrane on top of a 50 μm Pt wire. (C–E) Changes in temperature, lactate, pH measurements, lactate and sodium levels during the experiments. Reproduced from ref. 49 with permission from [Elsevier], copyright [1969].

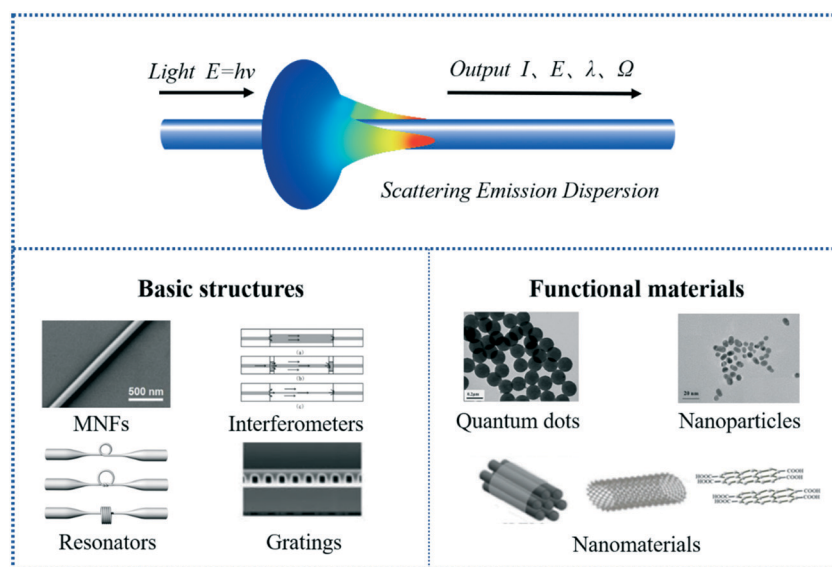


Fig. 4 The basic structure, functional materials, and signal conduction used by the MNF sensor.

Pan *et al.*<sup>22</sup> developed a skin-shaped wearable optical (SLWO) sensor that could be fitted tightly to human skin *via* a sensing patch. The SLWO sensor could also monitor the angle of bending in a wide dynamic range that can regulate the sensitivity. Adjustable sensitivity (0.01 to 0.47%) was used for bending sensing, as well as high resolution for temperature detection so that it could monitor breathing, arm movement, and body temperature in real time. Zhu *et al.*<sup>59</sup> proposed a stretchable wearable sensor of self-assembled wavy optical

microfiber. The optical sensor had high sensitivity and good repeatability, which depended on the microfibril characteristics of the microfiber. Guo *et al.*<sup>60</sup> reported a stretchable fiber Bragg grating-based optical (SFO) strain sensor interrogated by a free-running, dual-comb fiber laser. The manufacture and detection of the SFO sensor could be seen in Fig. 6. It had the ability of compliance, a highly scalable and flexible substrate, in line with curved and soft human skin, which could be used to monitor body activities. This sensor could



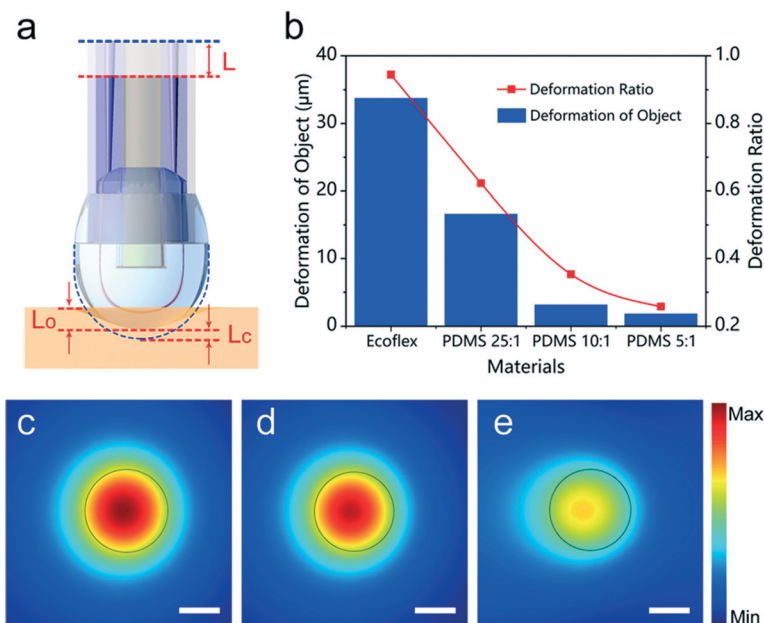


Fig. 5 (a–e) Schematic and simulation of the deformation of the compact tactile sensor and calculated intensity distributions of electric field guided by different diameter MNF. Reproduced from ref. 58 with permission from [American Chemical Society], copyright [2021].

be assembled on a suit or mounted directly on different parts of the human skin. Different human activities could be monitored in real time, including not only subtle movements, such as sound, breathing, and facial muscle movements, but

also large-scale movements, such as marching, jumping, squatting, twisting joints, and bending.

Currently, many researchers explore this technology because of its cost effectiveness, fast response, ultra-high

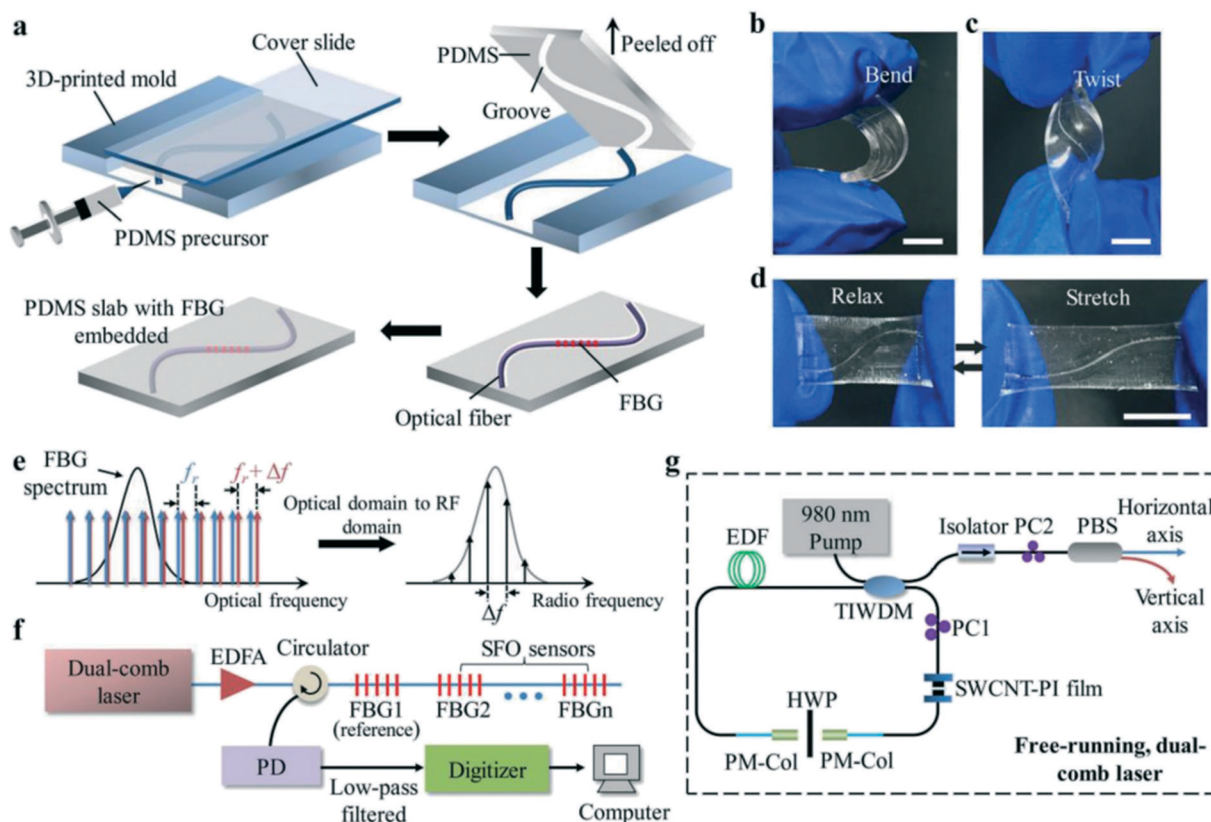


Fig. 6 (a–g) Fabrication and interrogation of the SFO sensor. Reproduced from ref. 60 with permission from [John Wiley and Sons], copyright [2019].



sensitivity and low consumption, portability, accessibility, and simplicity or ease of use in clinical environments. Pan *et al.*<sup>61</sup> designed a wearable flexible liquid filled fiber adapter (FLFFA) optical sensor that was sensitive to mechanical stimulation. The new FLFFA sensor was composed of two quartz fibers and a liquid-filled hose. In the presence of a liquid core, FLFFA had reconfigurability and adjustability in sensitivity in properties. By bending or squeezing, the tube was deformed, which could cause a variation in light transmittance to being wavelength insensitive. Thanks to the signal recording system equipped with LED charge coupled device (CCD), 12 FLFFA output signals can be measured simultaneously.

Optical sensors have extraordinary potential in a wide range of clinical measurements and detection.<sup>62,63</sup> However, the adjustable optical performance and reconfigurable sensor structure of wearable optical sensors still have huge challenges.<sup>61,64</sup> Sometimes, through the optical interface of the sensor, the skin provides a path from the hidden blood vessel structure and organs. Hence, it is necessary to evaluate the optical properties of skin, especially in the design of optical sensors.<sup>65</sup> Future research also could pave the improvement of measurement and detection.<sup>53</sup>

### 2.3 Bioelectrical impedance wearable sensors

In recent years, due to the popularity and development of wearable technology and mobile medical system, and considering the cost-effectiveness of remote health monitoring, these technologies have increasingly become the solutions of traditional medicine. In electricity, in a circuit with resistance, inductance and capacitance, and the blocking effect on alternating current (AC) is called impedance. Bioelectrical impedance analysis (BIA) is to use the conductive function of the human body to collect and measure the electrical impedance changes of tissues and cells through bioelectrical sensors, and then reconstruct the 3D mathematical model. Then, through the comparison of database samples, a comprehensive and scientific evaluation result of human current health status is obtained.<sup>66</sup> BIA has many advantages, such as non-invasion, risk-free, affordable, and simple structure.<sup>67</sup>

Yao *et al.*<sup>68</sup> designed a wearable electrical impedance tomography sensor with an elastic bandage and 8 electrodes were developed, and gesture recognition could be realized by a machine learning algorithm. Through the study of four kinds of electrodes, rectangular copper electrode was selected as the best electrode. Because the contact impedance engenders large noise, this would reduce the recognition rate in the measurement.<sup>69</sup> The researchers reduced the contact impedance by applying a certain amount of medical conductive fluid to the skin in contact with the electrode and increasing the contact area and pressure between the electrode and the skin. To improve the rate of gestural identification, the investigators also designed electrical models of electrode skin contact impedance, which contributed to an improved rate of gestural identification.

In the clinic, BIA is often used to estimate body fat, in principle by measuring electrical impedance in humans. There is some contact resistance between the electrode and skin invariably, and hence there is an impedance error in measurement, which leads to some errors in estimating the percentage of body fat.<sup>70</sup> To offset or reduce the effect of contact resistance, many commercial BIA human fat analyzers use electrodes large enough. Nevertheless, large size electrodes cannot be installed in wearable small devices, so it is becoming more and more important to use micro electrodes to accurately measure impedance.<sup>71</sup>

Jung *et al.*<sup>72</sup> reported a wrist strap bioelectrical impedance sensor with a micro electrode, which could be used for daily obesity management. The composition of the human body was analyzed by exerting a small alternating current on the body and gauging the impedance. The sensor could make up for the contact resistance of the current exerting electrode and the contact resistance of the voltage sensing electrode. Therefore, even if the electrode size was quite small, the human impedance could be accurately estimated. The measurement time of the wrist wearable bioelectrical impedance sensor was only 7 seconds and could be shortened ulteriorly. This type of sensor technology provided novel possibilities for future intelligent wearable sensor devices.

### 2.4 Resistive wearable sensors

Skin and mucous membrane are the first barriers protecting the human body, and particularly the epidermis plays a pivotal part.<sup>73</sup> The epidermis can protect the soft tissue from harmful radiation, and its base corner mold layer causes resistance due to its oily nature. Due to the rigidity of ordinary strain sensors, they cannot meet the requirements of wearable strain sensors.

Kim *et al.*<sup>74</sup> proposed a simple wearable high-sensitive resistive pressure sensor, which was composed of solid carbon composite conductors with irregular surface morphology, which can be seen in Fig. 7. The biggest feature of the sensor was based on a remarkably pliant and strong carbon composite conductor, which was fabricated by perpendicularly arrayed carbon nanotube and inserted in a polydimethylsiloxane matrix with an inordinance surface. The sensor could be used to detect various human locomotion, including fine blood pulses and active joint movement and could be applied to draw the spatial pressure distribution map in the multi-pixel platform.

Liao *et al.*<sup>75</sup> developed an advanced wearable sensor for human motion detection. The micro crack assisted resistance strain sensor could achieve a relatively high sensing performance. The researchers integrated the patterned polydimethylsiloxane with silver nanowires to construct a strain sensor with super sensitivity and large tensile property. The excellent sensitivity depended on the patterned design of specific surface microstructure, which was 136 times higher than that of ordinary sensors. The sensing mechanism depended on the change of resistance. When the mechanical deformation



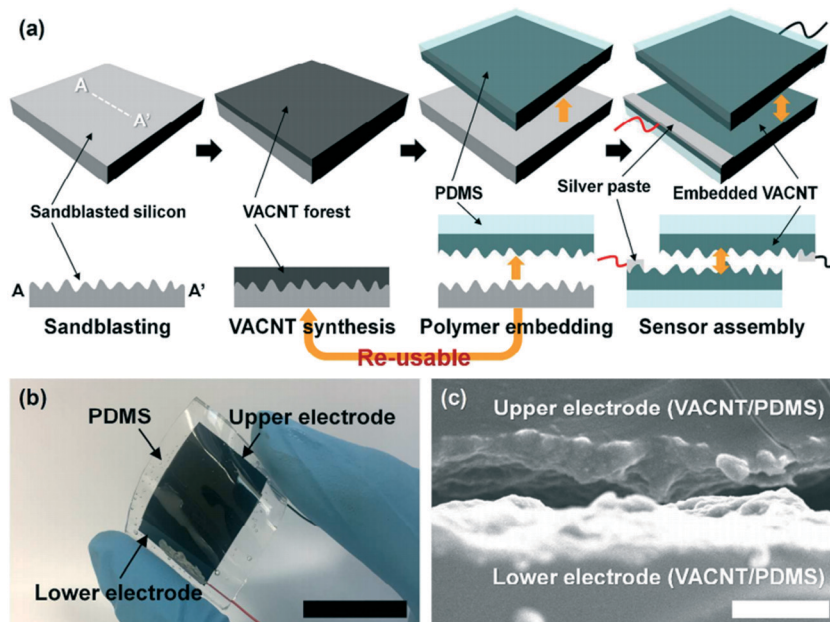


Fig. 7 (a–c) Schematic illustration and material topography of a simple wearable high-sensitive resistive pressure sensor. Reproduced from ref. 68 with permission from [American Chemical Society], copyright [2017].

strain was concentrated, the change of resistance was significantly affected by the surface microstructure of infiltration-microcrack. The sensor had excellent sensing, low creep, tensile and ultra-high stability.<sup>76</sup> Because the signal of the resistance sensor is easy to collect, and the sensor structure is simple and easy to manufacture, it has also been widely used in pressure sensors in recent years.<sup>77,78</sup> This simple, low-cost, and stable wearable resistance pressure sensor provides a certain direction and practicability for the advance of diverse wearable electronic products similar to skin.

## 2.5 The other wearable sensors

At present, several conductive materials with outstanding electrical and mechanical performances (such as graphene, carbon nanotubes, and metal particles)<sup>79,80</sup> have been combined with elastomer composite substrates with success to manufacture a few typical flexible sensors. Nevertheless, these devices still have unfulfilling sensitiveness and high mechanical stiffness.<sup>81</sup> Hydrogels are networks of hydrophilic polymer chains, sometimes called colloidal gels, where water is a dispersed medium. Due to inherent crosslinking, the structural integrity of the hydrogel network will not be dissolved by the high concentration of water. Hydrogels can be applied to wearable ionic devices by adjusting the toughness and fluidity of hydrogels.<sup>82</sup> The anti-freeze and anti-conductive hydrogels have been widely developed as a flexible wearable sensor, which enables being connected to the skin to monitor all kinds of human motions and subtle physiological signals momentarily.<sup>83,84</sup>

Nagamine *et al.*<sup>85</sup> reported a hydrogel based chemical touch sensor pad consisting of electrochemical L-lactic acid

biosensors, which could extract and analyze sweat compositions noninvasively. The working electrode of the sensor was entirely covered with agar hydrogel holding sweat extract. Sweating could be detected without exercise by temperature or cholinergic drugs. When the sensor touched the skin, agarose hydrogel could incessantly detect L-lactic acid from the sweat of the body.

There are a variety of other new wearable sensors to meet diverse applications. For example, the high-performance wearable strain sensor for tracking human joint movement and muscle vibration is developed in ethylene glycol hydrogels by covalent crosslinking polymers (Paam).<sup>86</sup>

## 3. Health monitoring

The flexible wearable skin-like sensors have the ability to monitor and record physiological signals in real time for a long time and have been widely used in the field of medical and health monitoring.<sup>87–89</sup> They can monitor the human body for a long time, continuously and in real time, with low burden, low discomfort, and high efficiency. Real-time collection and analysis of important physiological signals are the keys to realizing continuous and long-term monitoring of human health and personalized medicine. The skin-like sensor can be attached directly to clothing or skin to monitor the physical and chemical signals of the body's target in real time.<sup>90</sup> In order to be successfully used for long-term health monitoring of the body, in addition to a flexible base and high efficiency, skin-like sensors also need to be highly flexible with strong durability, low power consumption, and high extensibility. These requirements make the construction of sensors more demanding.<sup>91,92</sup> The flexible wearable skin-like



sensors based on different sensing mechanisms can be used to develop long-term, real-time health monitoring equipment. According to the different sensing mechanisms, the health monitoring equipment prepared can be used to monitor different human health indicators.<sup>93,94</sup> For example, wearable skin-like sensors based on optical sensing mechanisms are often used to develop sensitive and fast response blood oxygen monitoring instruments in the human body due to their advantages of good anti-interference, high sensitivity, and easy realization of multi-path or distributed sensors.<sup>95,96</sup>

To give an example of skin-like wearable sensors, Zhan *et al.*<sup>97</sup> created a flexible, wearable, and flexible skin-like pressure sensor based on a novel SWNT/tissue paper, which could monitor important physiological signals in real time, such as muscle activity and pulse changes at various positions of the body (Fig. 8). It could be used to detect the change of minute stresses caused by small amplitude motion (such as light touch, heartbeat, and breathing) and prevent the occurrence of related diseases. In order to obtain better performance, such as higher sensitivity and lower detection limit, a flexible substrate with microstructure is used to prepare pressure skin-like wearable sensors. On the other hand, the selection of active materials is also crucial to the chemical stability of carbon nanotubes, and there have been a variety of mature technologies for efficient mass production of novel SWNT, which could improve sensor sensitivity as well as stability, and reduce construction costs.<sup>98–101</sup> Flexible and wearable skin-like pressure sensors were made by impregnating single-walled carbon nanotubes in tissue paper and sandwiched between a bare PDMS sheet and a polyimide (PI) sheet with gold-forked electrodes. The construction method was simple while the cost was low, and almost no chemical reagents were needed. The typical sensitivity of  $2.2 \text{ kPa}^{-1}$  could be achieved in a wide range of 35–2500 Pa, and in the range of 2500–11 700 Pa, the sensitivity was  $1.3 \text{ kPa}^{-1}$ . It was shown that the method had high sensitivity over a wide range of pressures.

The skin-like pressure sensor could also be used as an artificial skin for the development of intelligent assisted robots that could measure the position and magnitude of pressure applied to the robot (Fig. 9). As can be seen from Fig. 9(b–f), the pressure sensor prepared in this experiment has excellent bending performance, and the flexible sensor array can detect the touched object sensitively and could quickly and sensitively identify the position and quantity of finger press. The principle was that when the finger touched the sensing area of the sensor, the matrix would make a quick response and reflect the signal on the monitor and showed the corresponding contact part on display. The response speed of the sensor array depends on the response speed of a single pressure sensor, so a large area of pressure sensing can be achieved without affecting the response speed, so that the shape of the touched object can be determined according to the contact area and quantity. This method has great application prospects in the development of low-cost artificial skin and wearable intelligent electronic products.

The skin-like wearable sensors are a cutting-edge method of wearable technology and are widely used in medical and health monitoring to help monitor the changes of various signals in the body and prevent the occurrence of potential diseases.<sup>88,102</sup> Skin-like sensor, because of its small shape, good biocompatibility, flexible substrate, and other properties, can be a “tattoo”, closely attached to the human skin surface. Thus, on the basis of not affecting the user’s daily life, it can continuously monitor a number of human health indicators so as to monitor the health status of the body.<sup>103,104</sup> Electronic-skin (E-skin) can mimic human skin, with tactile perception, temperature detection, pressure testing, excellent tensile resistance, and other functions.<sup>105</sup> Therefore, the E-skin sensor based on a flexible substrate has great application potential in many fields, including human health monitoring, surrounding environment perception, and the development of intelligent devices.<sup>106</sup> At present, this technology has been widely used in human health monitoring, such as measuring heart rate, blood pressure, pulse,

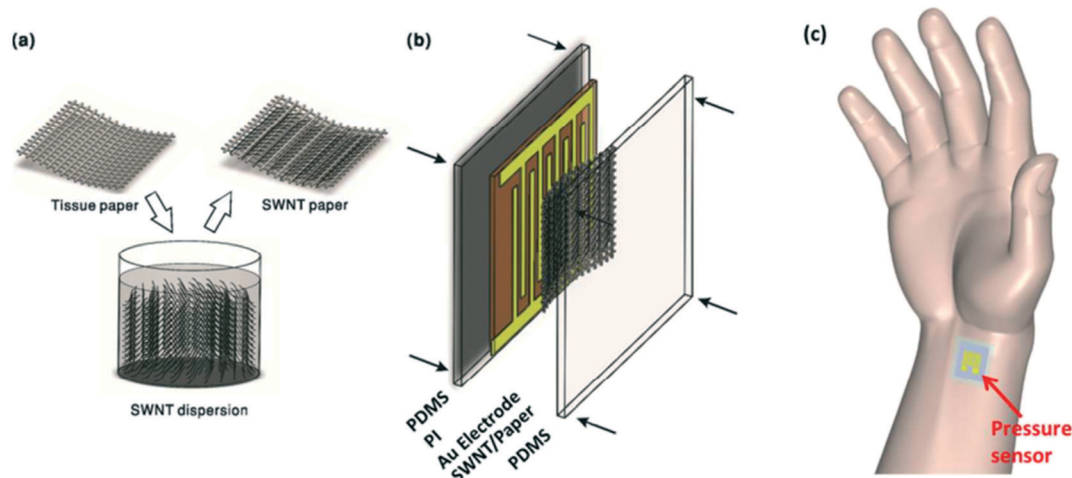
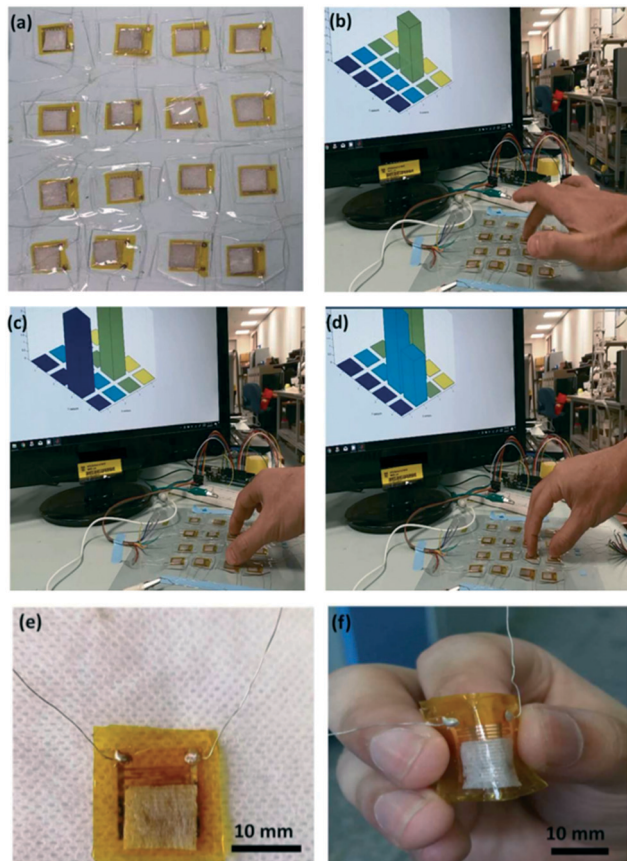


Fig. 8 (a–c) Schematic illustration of the fabrication process of a pressure sensor. Reproduced from ref. 97 with permission from [American Chemical Society], copyright [2017].





**Fig. 9** (a–f) A simple demonstration of flexible pressure sensor array as soft robotic skin. Reproduced from ref. 97 with permission from [American Chemical Society], copyright [2017].

temperature, and other human health indicators, and can quickly respond to the changes in health indicators and even realize the early prevention and diagnosis of diseases.<sup>107</sup> Chhetry *et al.*<sup>108</sup> designed a dual-function sensor platform with high sensitivity for temperature and strain that can adjust the function of E-skin sensing based on materials with outstanding electrical properties, such as black phosphorus and laser-engraved graphene (BP@LEG). Fig. 10 shows the diagram of multifunctional BP@LEG based E-skin sensor, preparation schematic, and structure characterization results of the materials with outstanding electrical properties, and demonstrates that the E-skin sensor had been successfully prepared. This E-skin sensor showed a high temperature exponent of 8106 K (25–50 °C) with high strain sensitivity (*i.e.*, gauge factor, GF) of up to 2765 (>19.2%), ultralow strain resolution, and longer durability. The good performance of the sensor satisfies the needs of E-skin, which provides a unique technical method and wide application prospects for human health monitoring and the development of multi-functional intelligent devices attached to E-skin.

The skin-like wearable sensors have been widely used in personal health monitoring of geriatric disease patients, improving the elderly life quality of patients, and reducing the family medical burden.

### 3.1 Common ion and molecular concentration monitoring

The skin-like wearable sensors can be used for long-term, real-time monitoring of common ion and molecular concentrations in elderly patients with diseases, such as pH,<sup>109,110</sup> glucose,<sup>111</sup> drug molecules,<sup>112,113</sup> *etc.* Under the regulation of the nervous system and body fluids, the normal body maintains a relatively stable internal environment through the coordinated activities of various organs and systems, so the pH in the body should be in a stable state. The base of traditional ion-selective electrodes lacks flexibility and mechanical flexibility, which makes it impossible to make close contact with the human body during the measurement process and thus cannot be made into a wearable device.<sup>114</sup> Many elastic materials are used to make flexible substrates for sensors, such as rubber, fibers, hydrogels, *etc.* Guinovart *et al.*<sup>115</sup> showed a wearable pH sensor using CNT-coated cotton yarn, which was used as a conductive substrate. Nyein *et al.*<sup>116</sup> reported a wearable skin-like electrochemical sensor that continuously monitored Ca<sup>2+</sup> and pH in body fluids using a multifunctional flexible sensor array that interfaced with a flexible printed circuit board, and its structure schematic diagram is shown in Fig. 11. The platform has been successfully used for real-time quantitative analysis of specific ion concentrations in body fluids such as sweat, urine, and tears. Results displayed in Table 2 show the Ca<sup>2+</sup> concentrations and pH in sweat and urine measured by the wearable flexible sensor array, ICP-MS, and Ca<sup>2+</sup> selective sensors. Ca<sup>2+</sup> acquired by sensors vary by a maximum 7.0% and 10%, respectively, from ICP-MS results. On the other hand, pH sensors show less than 2.2% and 3.6% variations from a commercial pH meter. Therefore, the sensors can be successfully applied to analyze Ca<sup>2+</sup> and pH in sweat and urine. The sensors have the potential to be used to diagnose diseases such as primary hyperparathyroidism.

### 3.2 Blood glucose monitoring

Blood glucose levels are one of the key indicators of a person's health. The traditional method of measuring glucose is to collect blood samples by piercing the skin. This method is invasive and could increase discomfort. Studies have proved the correlation between glucose concentration in sweat and blood glucose concentration.<sup>117</sup> Sweat could be used as the best experimental sample for noninvasive detection of blood glucose concentration. Glucose wearable sensors could realize rapid and noninvasive detection of glucose in sweat. Kim *et al.*<sup>111</sup> reviewed the research progress and challenges of non-invasive skin-like electrochemical glucose sensing systems and demonstrated that human glucose had been successfully monitored using skin-like electrochemical sensors on the skin surface. This skin-like electrochemical biosensor successfully overcomes the shortcomings of traditional skin puncture methods and minimally invasive subcutaneous glucose biosensors, providing hope for blood glucose control in elderly patients with diseases.



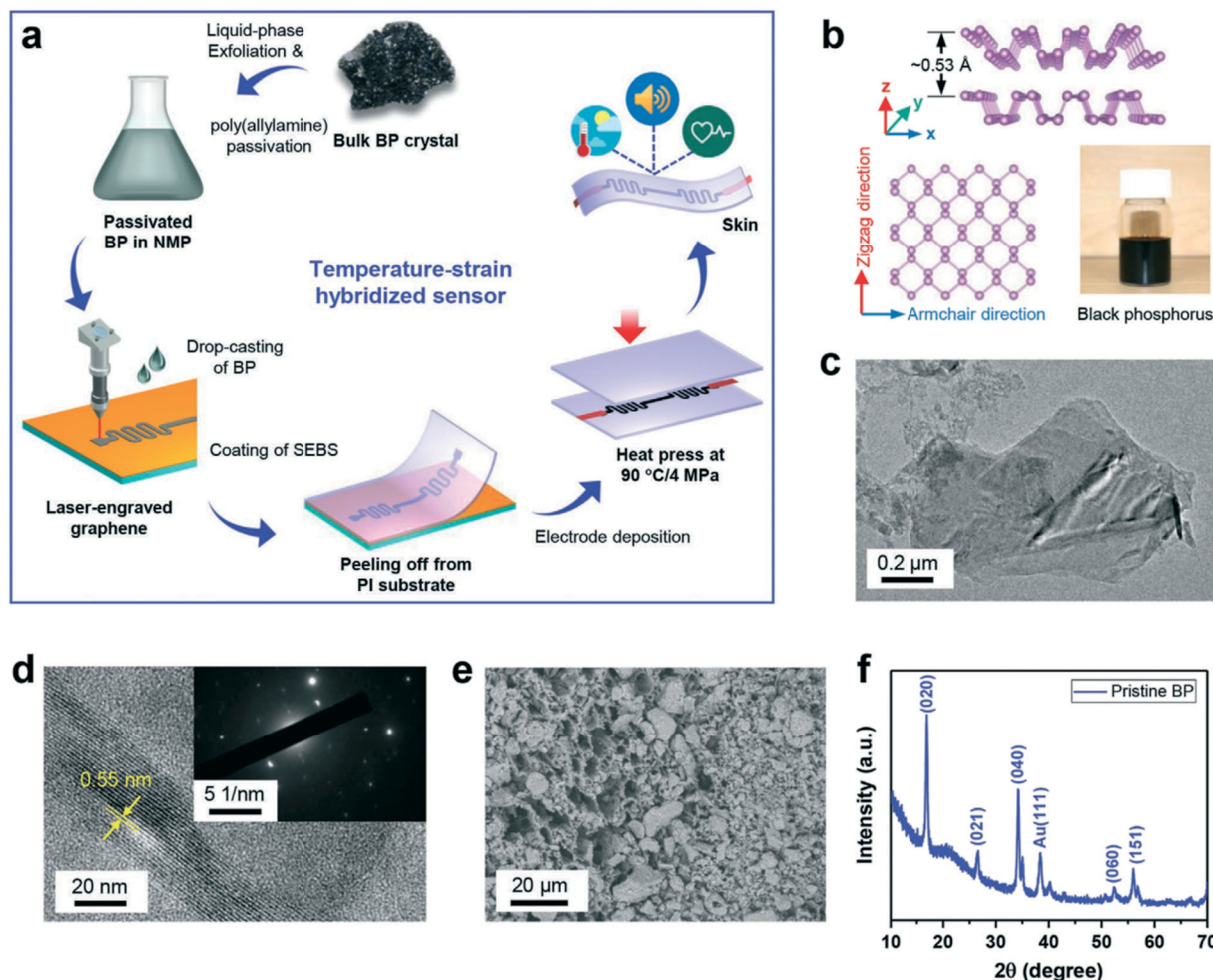


Fig. 10 (a–f) Schematic diagram of multifunctional BP@LEG based E-skin sensor and the preparation schematic and structure characterization results of the materials with outstanding electrical properties. Reproduced from ref. 108 with permission from [John Wiley and Sons], copyright [2020].

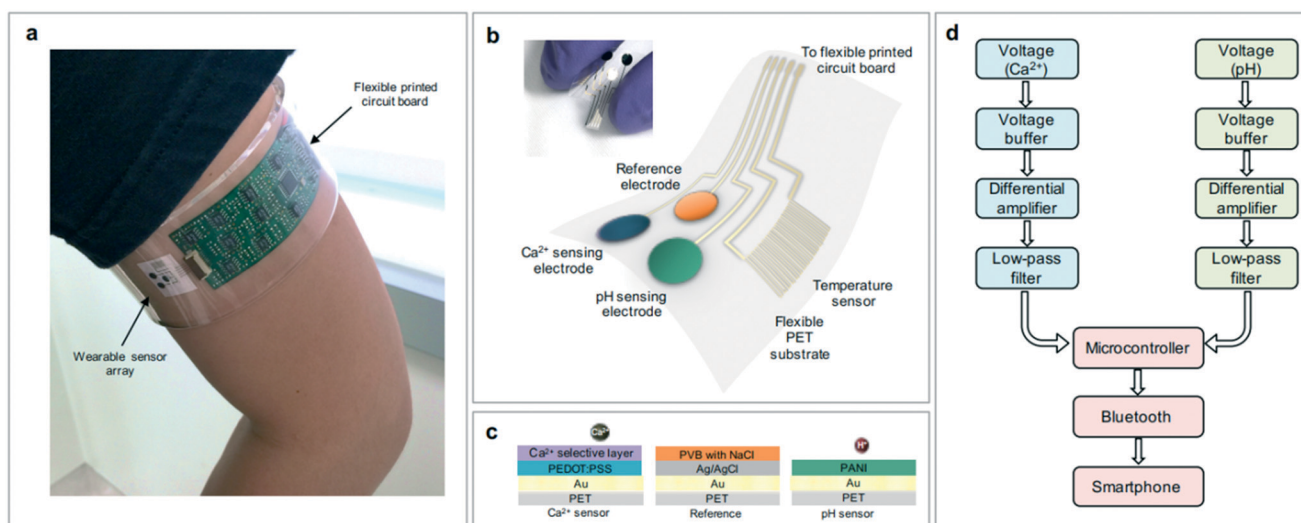


Fig. 11 (a–d) Schematic diagram of the structure and circuit board system of the wearable flexible sensor array. Reproduced from ref. 116 with permission from [American Chemical Society], copyright [2016].



**Table 2**  $\text{Ca}^{2+}$  concentration and pH in sweat and urine were measured by the wearable flexible sensor array and compared with ICP-MS and commercial pH meter measurements. Reproduced from ref. 116 with permission from [American Chemical Society], copyright [2016]

	$[\text{Ca}^{2+}]$ (mM)	$\text{Ca}^{2+}$ sensor	pH	pH
	$\text{Ca}^{2+}$ sensor	ICP-MS	pH sensor	pH meter
Sweat 1	0.96	0.92	4.4	4.5
Sweat 2	0.48	0.48	7.2	7.3
Sweat 3	0.76	0.71	8.1	8.1
Urine 1	1.8	1.8	7.6	7.8
Urine 2	7.2	7.1	6.3	6.5
Urine 3	1.2	1.1	6.4	6.6

### 3.3 Drug concentration monitoring

In addition to pH and glucose monitoring, drug monitoring also plays an important role in health monitoring. Drug monitoring relies on traditional blood analysis or urine analysis techniques, but these methods cannot provide real-time, on-site monitoring results and consume a long time and high cost.<sup>118</sup> In this case, the development of skin-like wearable sensors for drug monitoring has great application prospects. The drug levodopa (L-Dopa), which treats Parkinson's disease, could be monitored using a skin-like wearable sensor. Goud *et al.*<sup>113</sup> reported a continuous, minimally invasive microneedle sensing platform for cross-electrochemical monitoring of L-Dopa. This novel microneedle sensing platform was based on the construction of microneedles with different functions on the same sensor array patch to detect L-Dopa simultaneously and relatively independently using enzyme and non-enzyme voltammetry. L-Dopa was detected by square wave voltammetry and timing amperometry on unmodified and tyrosinase-modified carbon paste microneedle electrodes, respectively. The design and excellent analytical performances of the new wearable microneedle sensor array provided considerable application prospects for reliable, continuous, and minimally invasive monitoring of L-Dopa for the effective management of drug use in patients with Parkinson's disease. More importantly, the method had great potential for drug monitoring for other diseases of the elderly.

### 3.4 Body temperature monitoring

In addition to monitoring specific ions and molecules in the body, skin-like wearable sensors can also monitor body temperature.<sup>119</sup> In addition, temperature sensors can be integrated into other sensor arrays to address the impact of temperature changes during monitoring.<sup>120</sup> Trung *et al.*<sup>121</sup> prepared a skin-like wearable temperature sensor based on freestanding single reduction graphene oxide (rGO) fiber, and its structure and basic characteristics are shown in Fig. 12. In this experiment, a kind of independent, wearable, temperature-responsive rGO fiber with adjustable heat index was obtained by a simple wet-spinning method and by controlling the reduction time of GO. This independent temperature sensor based on optical fiber has good performance, such as high responsivity, fast response time (7 s), and fast

recovery time (20 s) to temperature. On the basis of high responsiveness, the sensor can also maintain good mechanical deformation ability. This method had great application potential in the field of medical care and real-time medical monitoring. It could be used to continuously monitor the postoperative temperature changes of elderly patients with diseases and assist in clinical drug use.

### 3.5 Cardiovascular health indicators monitoring

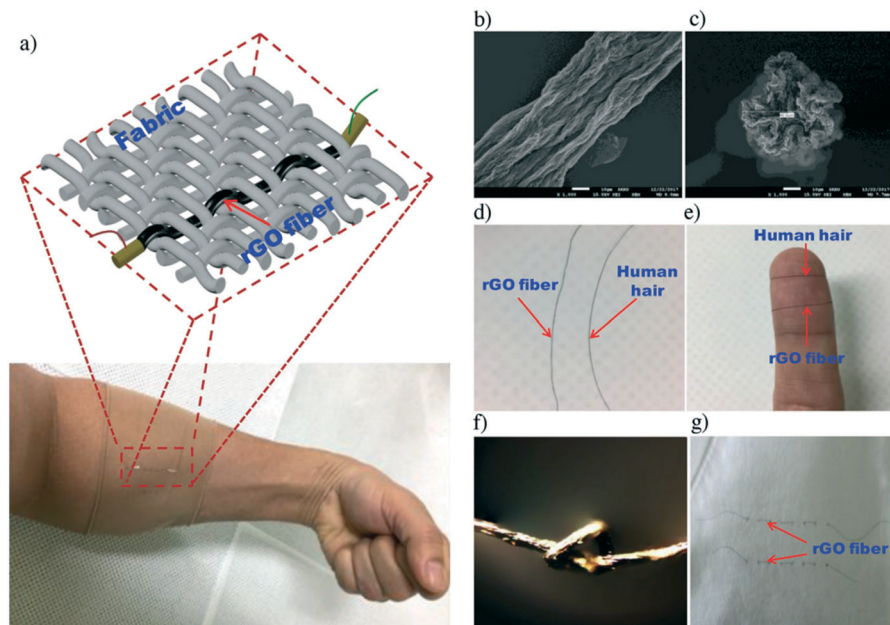
The use of skin-like wearable sensors to monitor a user's heart rate, blood pressure, oxygen saturation, pulse, *etc.*, has been widely reported and can be used for health monitoring of the occurrence and development of cardiovascular diseases.<sup>122,123</sup> The technology is ripe for use in the field of aftercare for elderly patients with geriatric diseases. For example, Chen *et al.*<sup>124</sup> developed a skin-like self-supplied voltage sensor based on hierarchical elastomer microstructure based on the strategy of adjusting the performance of self-supplied voltage sensors with different spatial densities. The sensor allowed continuous, long-term monitoring of the health of the heart and blood vessels and has been successfully used in continuous measurements of arterial stiffness, blood pressure, and the heart to assess cardiovascular health. The sensitivity could reach 7.989 V  $\text{kPa}^{-1}$ ; the working pressure range was across 0.1–60 kPa; the response was fast (40 ms); the signal-noise ratio was high (38 db); the stability was high. These good performances ensured its successful use in health monitoring of the cardiovascular status of the body. The sensor had the advantages of low cost, miniaturization, light weight, and low burden, and had great potential in the fields of medical care and intelligent auxiliary equipment development.

In addition to the above applications, the skin-like wearable sensor can also be used for the monitoring of bioelectrical signals, basic metal ions, body fluid specific molecules, *etc.* At present, more and more wearable sensors with high sensitivity, high specificity, and diverse functions have been reported, while wearable sensor technology in the field of medical monitoring has been more and more mature, but it is widely used in geriatric diseases in the elderly, and there are still some challenges yet breakthroughs, such as the elderly acceptance, degree of difficulty operating procedures, fully functioning, *etc.*

## 4. Intelligent auxiliary

Due to its characteristics of non-invasive, long-term use, portability, high biocompatibility and high detection accuracy, skin-like sensors with better performance are developing rapidly.<sup>125,126</sup> In the implementation of the human body physiological signal monitoring, comprehensive building real-time man-machine control systems, movement state monitoring system, development pressure contact auxiliary equipment such as intelligence have excellent application prospects.<sup>127–130</sup> Similarly, skin-like sensors based on different sensing mechanisms can be used to develop intelligent assistive devices with different functions.





**Fig. 12** (a–g) The architecture and fundamental characteristics of the freestanding fiber-based wearable temperature sensor. Reproduced from ref. 121 with permission from [John Wiley and Sons], copyright [2018].

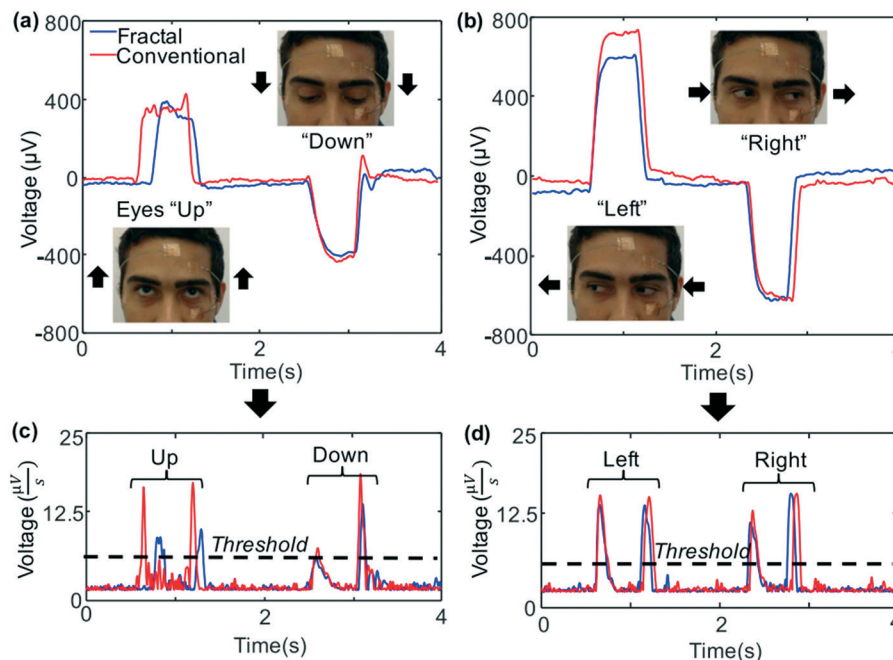
Wearable skin-like sensors because of its shape characteristics, on the one hand, can fit closely on the human skin surface, according to the joint parts to determine the need to detect indicators, such as in the inner wrist using skin-like sensors can be used to monitor the body heart rate, pulse, blood oxygen index, *etc.*,<sup>131,132</sup> and then through a simple data cable or Bluetooth connection with the mobile phone or computer terminal link.<sup>133,134</sup> The detection signal received by the terminal can be processed twice by specific software or programs; for example, the change of the detection index is drawn into a broken line graph, so that the users can intuitively observe the changes in their own indicators, so as to achieve intelligent monitoring of human health, so as to prevent the occurrence of disease early.<sup>135–137</sup> At present, smart watches have been widely put into the market, with a variety of functions such as monitoring sleep, heart rate, and running status, but there are still some aspects that need to be further improved, such as battery life, detection accuracy, and cannot be used alone.<sup>138</sup> In addition, it can also be installed on the lumbar spine and cervical spine. The wearable sensor can accurately and in real-time record the signal of the user's sitting position through the bending deformation state, which is used to prevent cervical spondylosis and lumbar disc herniation, and guide a healthy lifestyle.<sup>139</sup>

On the other hand, due to its excellent performance, the skin-like wearable sensor can be used to develop a non-invasive intelligent man-machine detection interface, which uses the sensors to detect physiological signals of the body and connects with external receiving devices through Bluetooth, so as to realize the system interaction between people and devices.<sup>140–142</sup> For example, many of the current elderly patients may end up bedridden and unable to move

or express their thoughts. Mishra *et al.*<sup>143</sup> designed a human-computer interaction system combining skin-like sensors and Bluetooth components and connected the sensor components to the smart wheelchair chain. Tightly on the skin around the eyes by the skin-like sensors, monitoring the movement of the eye, and will be collected by wireless transmission signals to the data collecting unit for signal processing, and then according to the preset program realization of a wheelchair intelligence operation, as shown in Fig. 13, such as eye upward movement, the wheelchair to go forward, down to stop movement, left for counterclockwise, for clockwise rotation to the right, *etc.* This human-computer interaction system, which can detect human data and control wheelchairs wirelessly in real time, shows great potential in the field of preparing long-term wearable and clinically applicable human-computer interaction intelligent assistive devices.

Recently, devices that use photoplethysmography (PPG) to detect heart rate in real time have become popular.<sup>144–147</sup> It is inexpensive and non-invasive to obtain various parameters that facilitate monitoring and control of exercise intensity. The PPG sensor wearing on the wrist showed satisfactory readings than wearing on the rest of the body.<sup>50</sup> The most popular form of wearable electronic device is a wristband smartwatch equipped with a PPG sensor that senses changes in blood volume associated with the heart cycle, acquiring a wide range of information, including heart rate (HR), peripheral oxygen saturation, and respiratory rate.<sup>148–150</sup> However, one of the key drawbacks of PPG sensors is the noise error caused by physical motion artifacts.<sup>16,151–154</sup> However, there are still significant differences in the accuracy of optical heart rate sensors in different physical activities. Specifically, the device is more accurate in sedentary behavior than active exercise.<sup>12</sup> Therefore, care should be





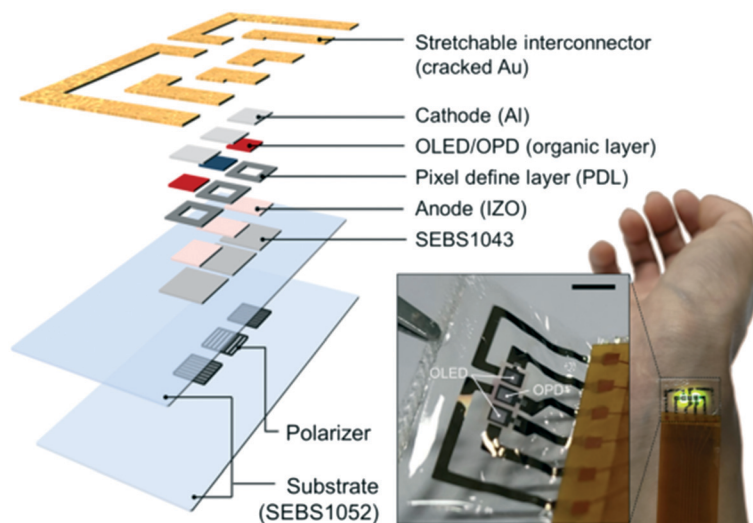
**Fig. 13** (a–d) A representative set of EOG signals involving four kinds of eye movements. Reproduced from ref. 143 with permission from [Elsevier], copyright [2017].

taken when using wrist band optical sensors to monitor real-time heart rate during aerobic exercise.<sup>50</sup>

Lee *et al.*<sup>155</sup> developed a skin-attachable PPG sensor with an orthogonal polarizer-analyzer (OPA) pair to reduce the amount of scattered light from the epidermis, which is the main cause of motion artifacts. The schematic diagram of the OPA sensor is shown in Fig. 14. The sensor, with two orthogonal polarizers, could successfully monitor PPG signals during wrist angular movements corresponding to physical activity, thus achieving continuous monitoring of individual daily

health care activities. Getting high-quality PPG signals during physical activity can diagnose a variety of cardiovascular-related diseases.<sup>156</sup> There are still significant differences in the accuracy of optical heart rate sensors in different physical activities. Specifically, the device is more accurate in sedentary behavior than active exercise.<sup>16</sup> Thus, caution should be exercised when monitoring real-time heart rate during aerobic exercise using wristband fitness equipment.

Xu *et al.*<sup>157</sup> reported on an ultra-thin and comfortable electronic device that integrated tactile stimuli,



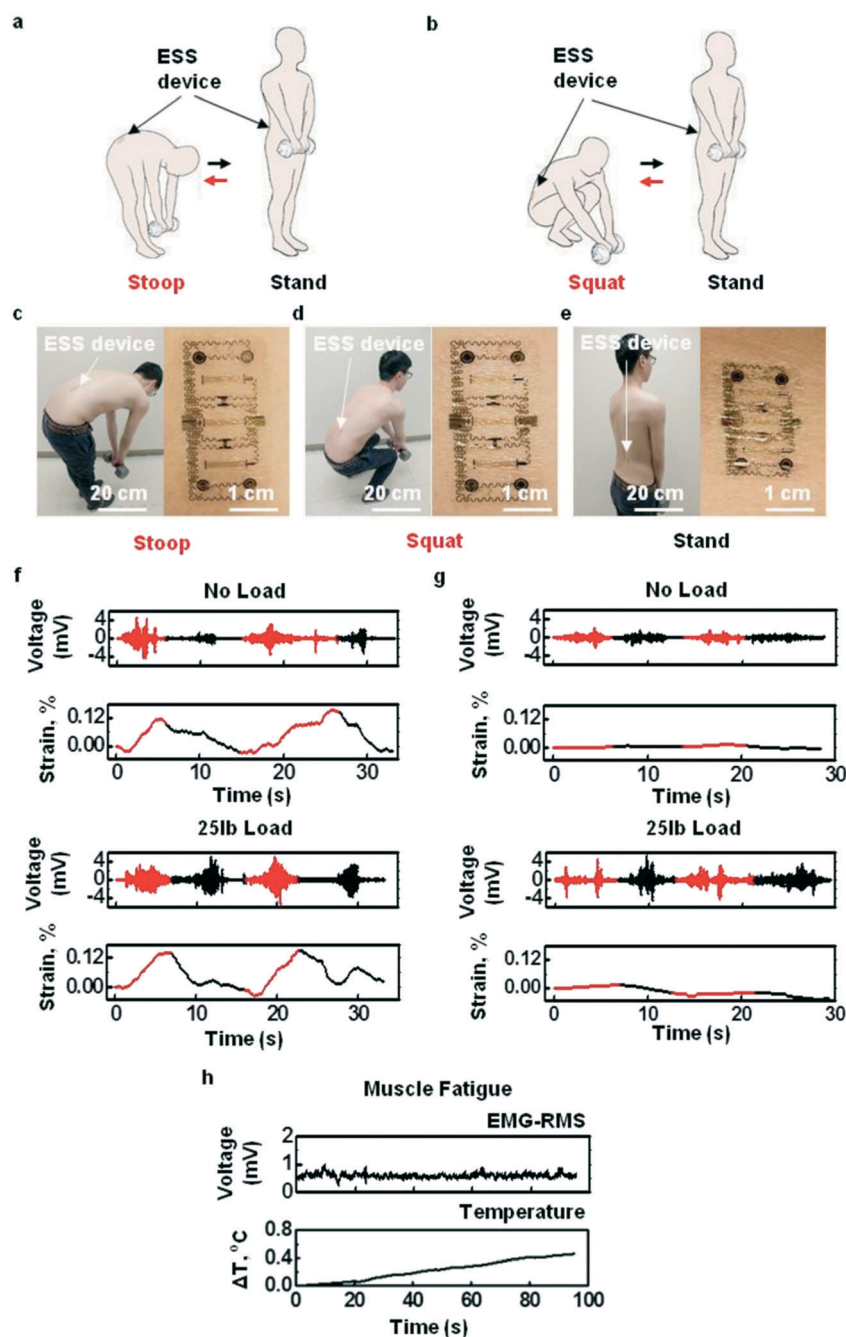
**Fig. 14** Schematic diagram of the layered layout of OPA sensor and retractable patch sensor in contact with the inner skin of wrist (scale bar, 3 mm). Reproduced from ref. 155 with permission from [Science], copyright [2022].



electromyography, and temperature and strain sensors on a simple platform. The metabolic response to the corresponding increase in skin temperature is related to the increase in blood flow. At this time, the temperature sensor could provide a reliable index of muscle strength and an important index in monitoring muscle fatigue. Fig. 15 shows the denatured status and EMG and strain comparison of skin-like strain sensors worn by volunteers in three different body postures during weightlifting. It was observed that the EMG sig-

nal remained constant, but the temperature increased significantly with time.

The improved stimulation electrode of the device adopts a serpentine structure, which allows large strain deformation and covers a larger area, so as to stimulate multiple motion units. Therefore, as shown in the device with large-area electrodes for electrical muscle stimulation and corresponding experimental results (Fig. 16), the device could not only provide sensory input to the body, but it could also induce



**Fig. 15** (a and b) Assessment of exertion and posture of the lower back during lifting. (c–e) Observed deformation during bending, squatting, and standing when the skin-like strain sensor is worn on the muscles of the lower back. (f–h) The EMG and strain comparison at different body postures and simultaneously recorded lower back EMG-RMS and temperature signals during muscle fatigue. Reproduced from ref. 157 with permission from [John Wiley and Sons], copyright [2015].



muscle contractions by increasing current levels. This has potential applications in the recovery of paralyzed limbs in patients, the assessment of neuromuscular function in athletes, or strength training.<sup>158</sup>

A device installed on the patient's lower back allows simultaneous monitoring of temperature, strain, and electromyography as an indicator of force and provides stimulus feedback to prevent overextension. In this study, a 22-year-old male was fitted with a device (right lumbar paraspinal area) on his lower back that simultaneously monitored multiple physical and chemical signals and recorded motor skills. The bending action will cause the characteristic response of the strain gauge, which is different from the squatting position. The electromyography and strain measurement results of different movements were summarized. Compared with a no-load condition, the EMG activity under load condition is significantly increased, which indicates that the equipment has the ability to detect load lifting. Through a series of experiments, researchers have shown that multiple operation modes of this type of equipment can be used simultaneously in sensory motor control, lower back motion monitoring, and muscle stimulation of the robot system. It provides a valuable research direction and a basis for simultaneously recording physiological data and presenting the ability of nerve stimulation input.

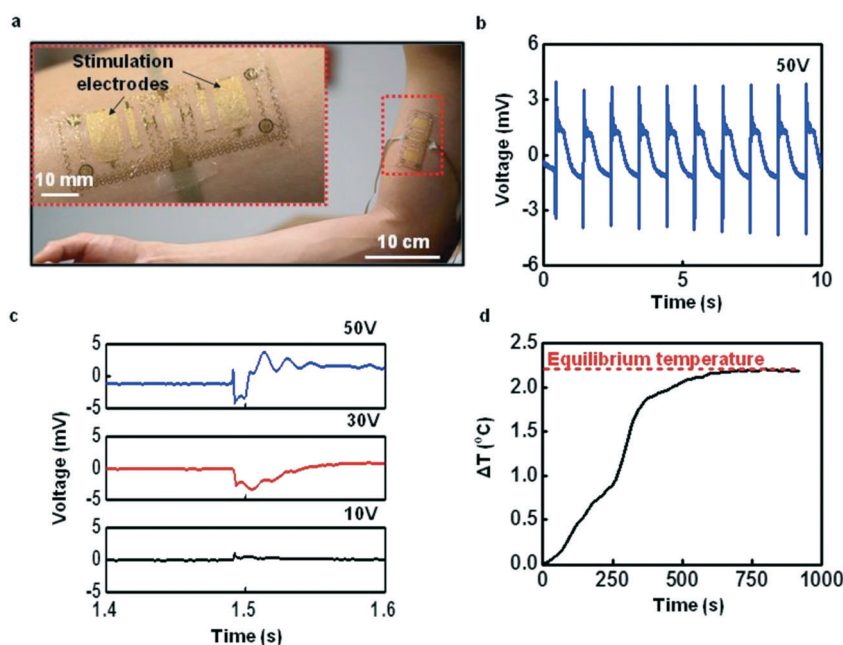
According to the current smart device market demand, the skin-like sensor has a good application prospect in the construction of intelligent motion monitoring systems. Because of its rapid response, flexibility, and quantitative analysis of physiological parameters, skin sensor can realize intelligent monitoring of athletes' training process and sports recovery

effect by performing real-time analysis of saliva and sweat in a non-invasive manner.<sup>163</sup> Although wearable sensor research and commercialization process has had the very big advance, but truly non-invasive intelligent device commercialization inevitably has a lot of challenges to be overcome in retaining high performance at the same time, need to study how to make it more diversified joint human body function, high efficiency range, equipment of retrieval, *etc.*<sup>164,165</sup>

## 5. Conclusion and future prospects

Due to their excellent performance, skin-like wearable sensors have become a very promising research field in recent years. In this paper, we summarized the recent progress of wearable sensors for skin samples in health monitoring and intelligent assistive devices, according to the different sensing mechanisms of the sensor, introduced a variety of wearable sensors used in health monitoring of the skin samples, including electrochemistry, biological impedance, and photoelectric sensors. In addition, because wearable sensors have flexible substrates and can be in close contact with the body, situ detection can be achieved, and extremely high sensitivity can be obtained. So, the application of wearable sensors in the development of intelligent auxiliary devices has a good development prospect, and relevant research results have been reported.

Because flexible skin-like wearable sensors have the advantages of transparency, good flexibility, strong stretching ability, free folding and bending, close fitting, *etc.*, they have great application potential in the fields of medical care and post-care for geriatric patients and have attracted more and



**Fig. 16** Device with large-area electrodes for electrical muscle stimulation. (a) Image of a device mounted on the biceps (magnified view, inset). (b and c) Example of evoked M-waves from induced contraction of the biceps at different stimuli. (d) Example of evoked M-waves from induced contraction of the biceps at different stimuli. Reproduced from ref. 157 with permission from [John Wiley and Sons], copyright [2015].



more attention. Although significant progress has been made in the field of geriatric health care, there are still some areas for improvement and challenges in the future. First of all, in order to achieve long-term and continuous monitoring of patients' body signals, the sensitivity of wearable sensors is highly required. Sensors convert light, heat, chemicals, or other signals into electrical signals, so wearable sensors need good electrical conductivity. In addition, the samples are usually sweat, saliva, or the subtle changes in the skin surface, and pulse. The complex composition, the number of monitoring signals, and some subtle movements of the body may make it difficult for wearable sensors to make efficient and accurate measurements. Introducing nanomaterials with good conductive properties can effectively improve the stability, sensitivity, and reliability of wearable sensors. More and more research results on nanomaterials have been published, but there are still problems to be solved in the selection of nanomaterials. Nanomaterials should not only have good stability, electrical conductivity, and sensing performance, but also biodegradable materials can be selected to prevent environmental pollution after a large number of preparations. Further research on the properties of nanomaterials can also be carried out to obtain better performance.

More importantly, the world is now experiencing lower fertility rates, longer life expectancy, more elderly people, and more diseases of old age. There are many challenges to overcome before skin-like wearables can be widely used in healthcare for elderly patients. For example, the cost, comfort, portability, and popularization of wearable devices need to be solved. While retaining high sensitivity and specificity, multiple sensing components should be integrated as much as possible to achieve multi-functional wearable devices, while reducing costs, improving comfort, and product aesthetics.

## Author contributions

Ziyu Huang: writing – original draft, conceptualization. Yaqi Xu: writing – original draft, conceptualization. Ya Cheng: investigation, conceptualization. Min Xue: investigation. Mengtian Deng: investigation. Nicole Jaffrezic-Renault: funding acquisition, writing – review & editing. Zhenzhong Guo: funding acquisition, conceptualization, supervision.

## Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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