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## Advanced and personalized healthcare through integrated wearable sensors (versatile)

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Due to people's hectic and intense working schedules, health as a priority is often pushed to the sidelines. This is more problematic for people with some health conditions, which require regular monitoring of vitals. Therefore, the development of smart diagnostics is a clinical challenge towards which, a lot of research is being carried out. This primarily includes the development of wearable sensors. These sensors can be worn by individuals for the monitoring of various biomarkers in different bio-fluids. Primary research is being carried out to make them sensitive, reliable, robust, and non/minimally invasive. Since the intended wearable sensor is to be used for continuous monitoring of the individuals, all the components required for the sensing must be on the same platform. This generally includes the sensing platform, microfluidic channels, and its electronic or optical components. The goal of the current review is to highlight the state-of-the-art integrated wearable sensors, describing their important components, methods of manufacturing, and applications of these sensors and discuss the challenges being faced while designing and scaling up these sensors. The contents of this review will help design and develop novel integrated wearable sensors that are expected to revolutionize the field of personalized healthcare.

### 1. Introduction

Busy schedules and long working hours have negatively impacted a lot of working professionals. As such, most individuals do not have sufficient time for simple routine check-ups. This is a serious issue since lot of diseases and conditions go unnoticed, creating problems at a later stage. Conditions such as strokes, coronary diseases, elevated glucose or other metabolite levels, cancer, *etc.*, can be fatal if left untreated. For instance, heart attacks are the leading cause of death worldwide, taking around 18 million lives a year.<sup>1</sup> The precious lives of people can be saved if the underlying situations or conditions are treated promptly. Since most people do not have access to standard or advanced healthcare settings, the pressing issue becomes aggravated. Taking healthcare solutions to patients in need becomes the most suitable option.

In this regard, wearable sensors become the key players.<sup>2</sup> Wearable sensors are non/minimally invasive analytical devices capable of providing point-of-care systems for the continuous and regular monitoring of individuals' physiological as well as

biological markers.<sup>3</sup> Unlike conventional point-of-care devices, wearable sensors can utilize easy-to-sample bio-fluids such as saliva, tears, and sweat for the detection of clinically important biomarkers. This combined with continuous or regular monitoring can help in timely intervention and preventative measures. Since these devices are autonomous, lightweight, and compact, their impact is barely noticed by the user in their daily life. As the data is transmitted wirelessly, this provides mobility and accessibility to the users/patients wearing these devices. This is particularly useful when monitoring neonates and elderly people. The wearable devices can be modified to provide personalized healthcare. The large amount of data obtained through these devices can be used to train machine learning algorithms, which can be helpful for decision-making through artificial intelligence. Though expensive currently, over time, these wearable devices will prove to be cost-effective. The concept of a wearable device is not new and has been in existence for a long time. The wearables used during the 1960s provided the foundation for today's next-generation wearable sensors. Fig. 1 shows the components of the wearable sensor, the biomarkers for which sensors are being developed, and the tremendous jump in the number of publications related to the development of wearable sensors over the years. The current wearables are capable of reliable continuous monitoring of an individual's vitals such as temperature, humidity, blood oxygen level, blood pressure, EEG, ECG, and many biomarkers of clinical relevance.<sup>4-9</sup> Apart from the sensing

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aspect, wearables also play an important role in the thermal management of the human body.<sup>10,11</sup> The electrochemistry-based transducer is the most reliable and flexible option available for the design of wearable sensors because of its sensitivity, ease of fabrication, no moving parts, mechanical robustness, and resistance to other conditions.<sup>12</sup> This transducer is the most widely used and trusted option for a biosensor.

Most of the research involving the development of wearable biosensors has been primarily limited to the fabrication and testing of the sensing platform *i.e.*, the development of a sensing surface for a particular physiological or biological marker. For instance, though a wearable sensor for cortisol has been developed, it still requires the use of an external potentiostat for the read-out.<sup>13–17</sup> There are many such examples. This essentially is against the concept of a wearable sensor. An ideal integrated wearable sensor should have the sensing platform and the associated electronics in a small and compact form that can be easily worn by the user.

The current review article is an attempt to stress the need for integration by briefly discussing the fabrication aspects of integrated wearable sensors using additive manufacturing technologies, the design and fabrication of multiplexed wearable sensors, and various microfluidic-based applications of

wearable sensors. Other than these, the review article will also discuss wearable multifunctional flexible sensors, strain sensors, pressure, and thermal sensors along with some discussion on the implantable sensors. This review will highlight the commercially available integrated wearable sensors and report the challenges encountered while designing and fabricating integrated wearable sensors. It will also provide future insights into the field of integrated wearable sensors.

## 2. Components of integrated wearable sensors

In order to understand the concept of integrated wearable sensors, it is important to know the different components that make up the integrated wearable sensors. The main parts of wearable sensors are sensors, which detect signals, signal conditioning circuits, which improve the signals, analog-to-digital converters, which convert analogue signals to digital format, microprocessors or microcontrollers, which process the data, memory, which stores the data, wireless communication modules, which transmit the data, power sources,<sup>18–20</sup> which supply energy, enclosures, which protect the sensors, and user



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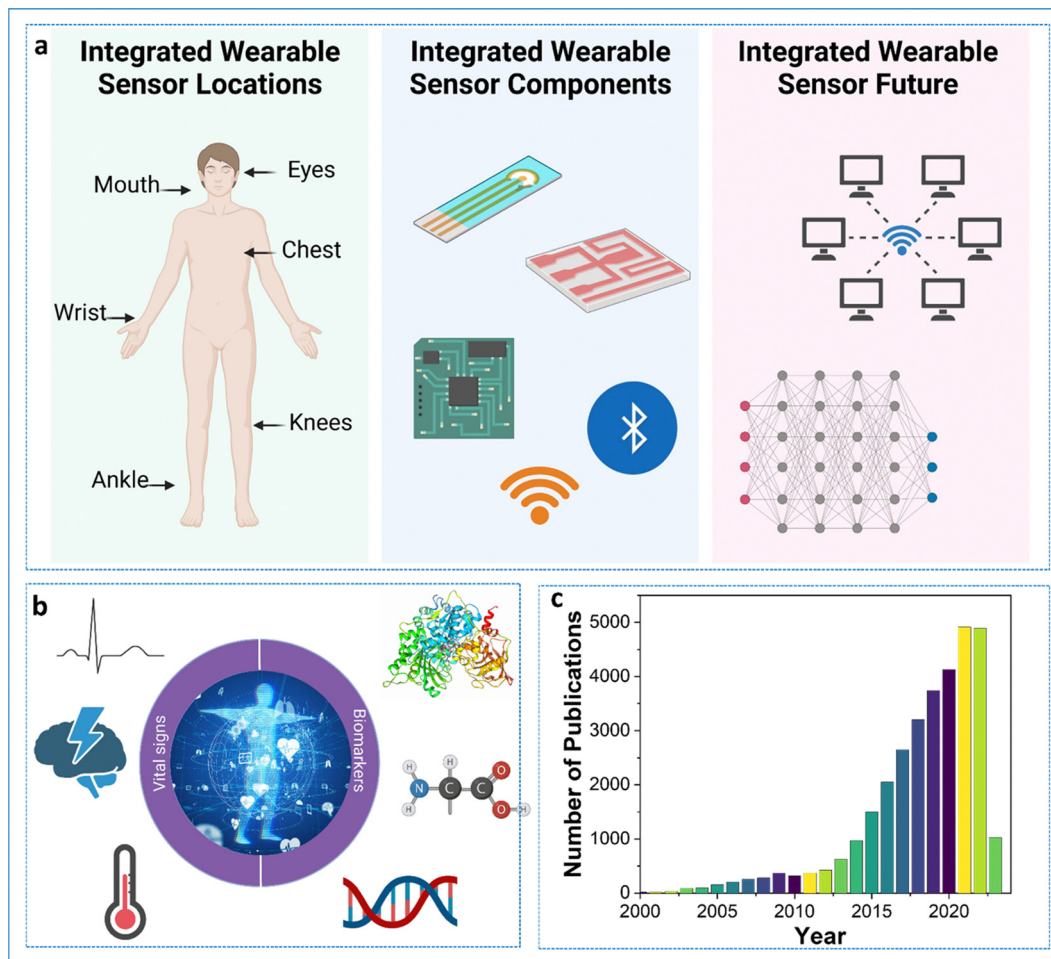


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**Fig. 1** (a) The various body parts for which integrated wearable sensors have been developed. The center panel broadly represents the various components of an integrated wearable sensor. These generally include electrodes, microfluidics for fluid transport and delivery, communication systems, and controllers. The future of integrated wearable sensors is in data analytics, self-powered and autonomous systems. (b) Biomarkers and vital signs for which sensors can be developed. (c) Trends for the number of publications over the years starting from the year 2000. [Source: Web of Science search, keyword: wearable sensors] [Fig. a and b created using Biorender.com].



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His research mainly focuses on human-machine interfaces, including soft electronics implants, wearable sensors, and biosensors.

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interfaces, which allow for interaction. Together, these elements make it possible to track and analyze diverse physiological and environmental data, enabling applications for personalized healthcare and well-being.

Interactions between a target and a bio-recognition element are the guiding principle while designing a sensing platform. The targets present in the bio-fluid are transported to the sensing surface, where the interactions with the bio-recognition element cause a change in the electrical signal, thereby enabling their detection. The electrochemistry-based transducer is the most reliable and flexible option available for the design of a wearable sensor because of its sensitivity, ease of fabrication, no moving parts, mechanical robustness, and resistance to other conditions.<sup>12</sup> This transducer is the most widely used and trusted option for a biosensor. The electrical changes can be amperometric (change in current), voltammetric (change in potential), or impedimetric (change in impedance or resistance). For a typical biosensing surface, the surface of the electrode is modified with a bio-recognition element, which





can be an antibody, aptamer, enzyme, peptide, or molecularly imprinted polymers (MIPs).<sup>21–24</sup> Using bio-recognition elements is challenging since these need to adapt to the extreme conditions that are generally faced by wearable sensors. Of these elements, the use of an antibody or enzyme is less encouraged since these are the most vulnerable entities outside their physiological conditions. Nowadays, the use of peptides and MIPs is quite prominent since these are almost resistant to physiological conditions. As wearable sensors are intended for continuous monitoring of various biomarkers, the regeneration capability and biocompatibility of these recognition elements also need to be considered. It has been observed that biosensors targeting redox-active molecules are easily regenerated compared to non-redox-active molecules, such as proteins.<sup>25</sup> As a wearable biosensor is intended for continuous and long-term usage, the regeneration of the sensing element also needs attention. In an ideal situation, the sensing elements do not need to be replaced. The prolonged exposure of the complex media to the bio-recognition elements reduces their efficiency and therefore they need to be replaced. Since the regeneration of these elements is not possible in wearable conditions, this becomes a bottleneck. MIPs are an attractive alternative to solve this problem since these can be easily regenerated.<sup>26</sup> For instance, Gao's group showed the regeneration of a wearable metabolite and nutrient sensor based on MIPs. The sensor was regenerated by the application of an electrical potential for a very short time (less than 30 seconds). During the regeneration step, the electrode's surface gets altered so that it releases the bound analyte and becomes refreshed.<sup>27</sup>

For the fabrication of a sensor, a substrate is first modified with one of the above-mentioned bio-recognition elements. Since most of the wearable sensors developed are electrochemical transduction-based, the substrate is an electrode.<sup>25,28,29</sup> The successful modification of the substrate is a critical part of biosensor design. The electrodes chosen should allow efficient and easy modification with the bio-recognition element, should not get fouled, be bio-compatible, and provide excellent electron mobility for the detection of various biomarkers of interest. These electrode surfaces are then functionalized to immobilize the bio-recognition elements. The use of nanomaterials is quite prominent for the development of electrode materials. Nanomaterials have proven their potential over a long time. They allow for a high surface-to-volume ratio, good electrical and optical properties, and allow efficient immobilization of the bio-recognition elements.<sup>30–35</sup> In some cases, the catalytic activity of the nanomaterials has been utilized for the signal generation of electrically active metabolites such as amino acids, ions, or other analytes.

Another component of the sensing platform is the substrate or the platform itself. The wearable sensor should be conformal to the human skin and also the platform on which the sensor is to be fabricated must be flexible and soft. In this regard, many different materials have been explored. For instance, the use of PDMS is quite prominent since it is easy to handle, can be molded into any shape, microfluidic channels can be built on it and is soft on the skin and flexible. For instance, Singh *et al.* used a PDMS-based platform for the fabrication of a sweat

sensor for cortisol. The gold electrode was deposited on the PDMS and microfluidic channels were also created in the PDMS to allow for the transport of sweat to the sensing chamber.<sup>36</sup> Polyimide is another low-cost substrate for sensor fabrication. Though this material is not as soft as PDMS, a modified polyimide (PI) surface can be used directly as an electrode material. For instance, the Gao group has demonstrated that the PI surface can be altered using lasers to produce laser-induced graphene, which can then be used as an electrode material. The work reported the use of this Laser Induced Graphene (LIG) electrode for the detection of cortisol in sweat and serum.<sup>37</sup>

Various electrical components are required to make a wearable sensor work. The foremost is the battery to power up the sensing surface, integrated circuits, and read-out devices. For a typical sweat-based sensor, the induction of sweat through iontophoresis also requires power. The other important component is the integrated circuits (ICs), which manage the power delivery, potentiostat, data acquisition, and transmission.<sup>38,39</sup> Various filters are also used in an integrated wearable sensor to eliminate any noise and unwanted signals coming due to external factors or motion artifacts. The electrical components are also responsible for the data transmission onto a smartphone using Bluetooth. The electronic component of a wearable biosensor is fabricated on a solid PCB or sometimes on flexible substrates depending on the intended application.<sup>40</sup>

The limiting factor for a wearable biosensor is the power supply. Since these sensors are intended for continuous measurements and data transmission, they consume a lot of power. To date, most of the devices developed have an external battery to power them. However, an idealistic situation is that the sensors can power themselves. Self-powered wearable biosensors are next-generation wearable sensors, wherein the sensors rely on energy harvesting from bio-fluids.<sup>41</sup> Interested readers can refer to the detailed analysis of various self-powered devices by different researchers.<sup>41–45</sup> A notable work is the development of a battery-free powered wearable sensor based on zinc oxide nanowires.<sup>46</sup> The work reported the modification of zinc oxide nanowires with lactate oxidase. The flow of sweat on the nanoarrays caused a generation of DC electrical signal which corresponds to the lactate concentration in the sweat. The generation of an electrical double layer by the nanowires creates a potential difference.

The healthcare data generated by the wearable sensor is generally continuously transmitted to a smartphone a laptop or a server for processing. Since the amount of data generated is quite complex, various mathematical models are required to apprehend the data, so that the user can easily understand it. To achieve fast and accurate processing of the data, various models, and cloud computing have been utilized.<sup>47–51</sup>

### 3. Additive manufactured wearable microfluidic devices

The use of wearable electrochemical biosensors based on microfluidic systems has attracted a great deal of interest in



non-invasive monitoring. It is critical to developing an efficient, flexible, robust, and inexpensive microfluidic system fabrication technique. Additive manufacturing or three-dimensional (3D)-printing emerges as a lucrative technology for fabricating novel devices with complex geometries and high precision for various applications, including microfluidics systems, food, healthcare, and environment monitoring.<sup>52</sup> 3D printing obtained ample attention for developing innovative microfluidic systems because of its advantages over conventional fabrication. Conventional techniques for manufacturing microfluidic sensors are generally expensive, and a few materials are suitable, but a great variety of reproducible geometries can be prepared using 3D printing.<sup>53</sup> Also, polydimethylsiloxane (PDMS)-based epidermal microfluidic devices manufactured using the soft-lithography method require special facilities, such as a clean room with a UV lithography machine, and multi-step processing, which is lengthy and expensive.<sup>54</sup> 3D printing offers a high throughput and high-resolution fabrication of microfluidic devices.<sup>55</sup> Mainly the process of 3D printing involves solidifying materials with computer control to create objects in 3D.<sup>56</sup> However, several types of 3D printing such as including inkjet 3D printing (i3DP), fused deposition modeling (FDM), stereolithography (SLA), and two-photon polymerization (2PP) have been demonstrated to fabricate the microfluidic electrochemical sensor.<sup>57</sup>

The i3DP technique has been found to be the most commercially viable among the 3D printing methods.<sup>58</sup> To fabricate the microfluidic channel on a submillimeter scale, the i3DP approach has been widely taken. Typically, the i3DP approach relies on the continuous or drop-on-demand (DoD) mode.<sup>59</sup> For fabricating the micrometer scale of microfluidic devices, i3DP has become very demanding. Gowers *et al.* (2015) demonstrated a 3D-printed microfluidic device that can continuously monitor human tissue metabolite levels.<sup>60</sup> A needle-type biosensor integrated with regulatory-certified (FDA) clinical microdialysis probes through the use of a probe outlet holder, is shown in Fig. 2.<sup>60</sup> This novel and innovative structure minimizes the extra connection tubing and adaptors, thus miniaturizing the device size. Typically, to substitute the micro vial, the microfluidic device is inserted into the probe outlet holder. To mimic the configuration of the micro vial, an L-shaped 3D-printed

microfluidic chip was fabricated. The L-shaped design renders a miniaturized microfluidic chip.

Furthermore, fused deposition modeling (FDM) 3D printing has been widely used to fabricate elastomer-based microfluidic devices due to its low cost.<sup>61</sup> The FDM involves feeding and melting polymer filaments into a heated metal cylinder that ends with a nozzle and extrudes them.<sup>62</sup> Wei *et al.* (2022) demonstrated a novel precision-controlled 3D-printed tailored microfluidic channel using malt syrup (Fig. 3a).<sup>54</sup> The fabricated flexible microfluidic model combined with an encapsulated microfluidic channel layer for collecting sweat and a pH sweat sensor for sensing pH, as shown in Fig. 3a. The design involves several steps starting with the 3D printing of the sugar filament mold, encapsulation of the fabricated microfluidic channels, incorporation of the pH sensor, and encapsulation of the system. Microfluidic devices were mounted on the skin to collect sweat and analyze it as a proof of concept (Fig. 3b). As shown in Fig. 3c, the microfluidic device showed a good performance as its measured pH values matched the pH values of the commercial pH meter.

Though 3D printed microfluidic devices have many advantages still, their resolution is yet to be comparable with the devices made with the conventional lithography technique.<sup>58</sup> In addition to the device's resolution, some other issues include a lack of compatible materials, the roughness of the device's surface, layer-by-layer finish, and conformability with the skin.<sup>63</sup>

#### 4. Design and fabrication of multiplexed integrated wearable sensors

In recent years, there has been a sharp increase in demand for wearable sensors. The sensors that can be worn and able to track body temperature, bodily movements, blood pressure, and heart rate are already often utilized in daily life and are currently commercially accessible has revolutionized the field of health care.<sup>3</sup> However, to enhance the capabilities of wearable sensor efficiency and subsequently obtain more detailed data about the health of a wearer and physiological body

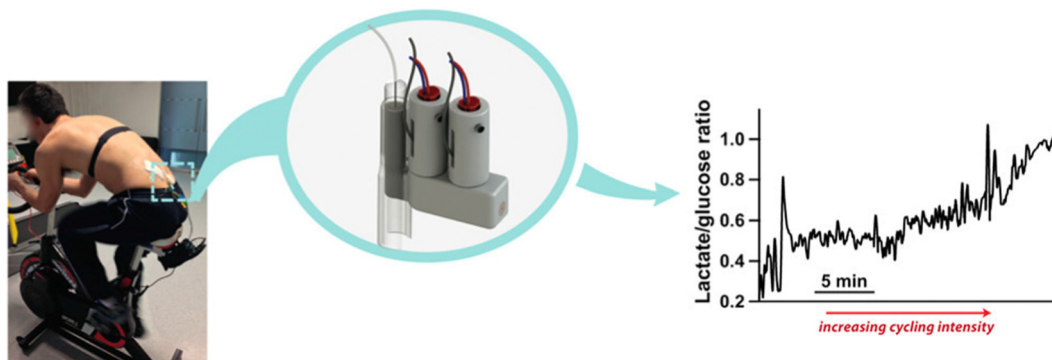


Fig. 2 A microfluidic system that measures lactate and glucose levels in dialysate during cycling.<sup>60</sup> Copyright 2015 American Chemical Society.



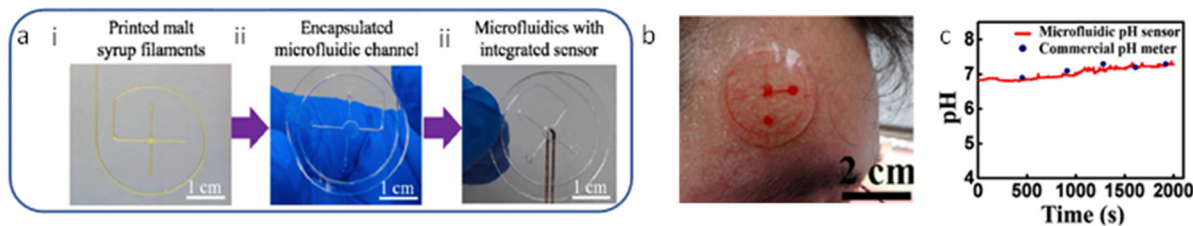


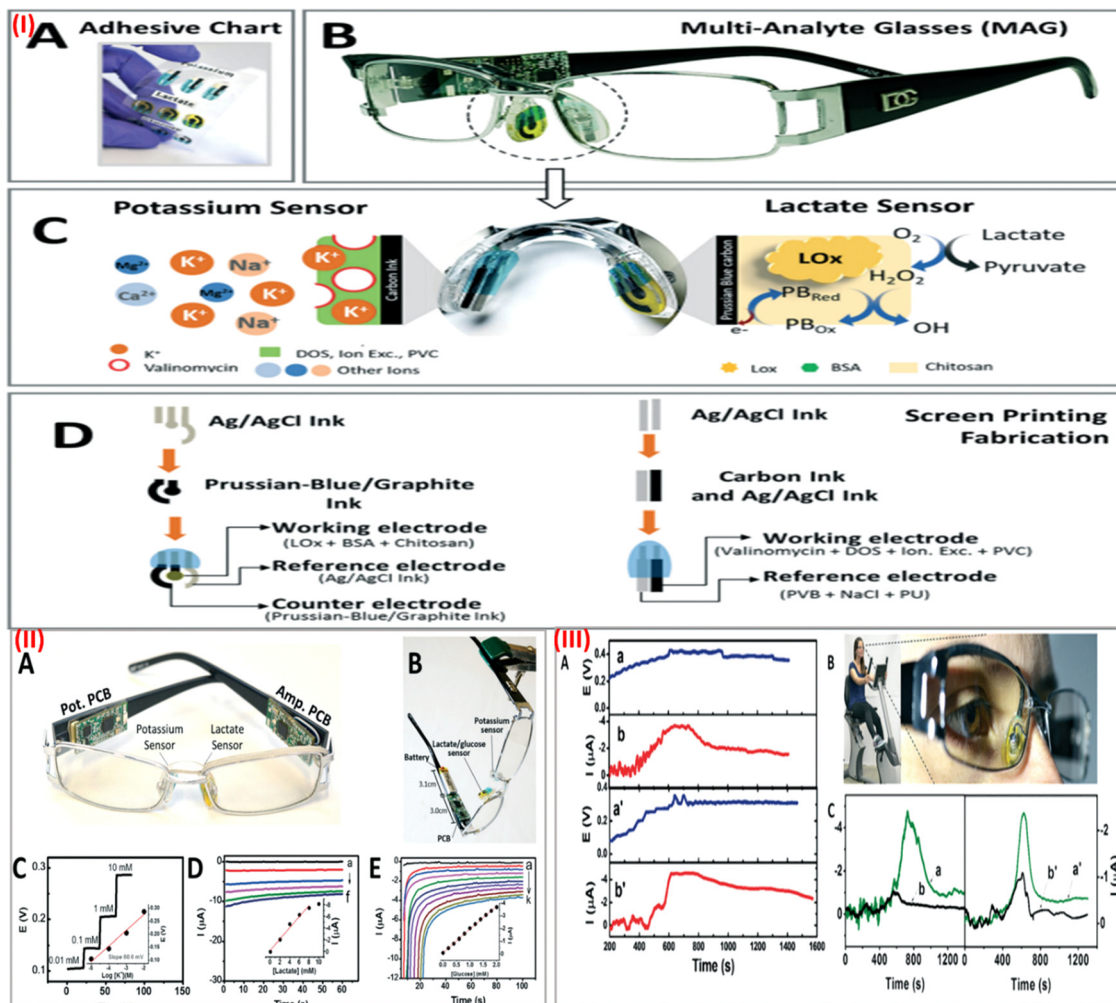
Fig. 3 (a) Steps (i, ii, and iii) involving manufacturing the microfluidic device and integration, (b) Photograph of the microfluidic chip onto the forehead for sweat collection, and (c) comparison of the real-time results between the commercial pH meter and the developed sweat pH sensor. Adapted with permission from ref. 54. Copyright 2022 Elsevier.

condition, novel non-invasive biometric sensors are very much needed.<sup>64</sup> Recently, several research studies have tried to fill this gap by developing wearable sensors that can track body metabolites like lactate, glucose, or uric acid as well as blood electrolytes like sodium and potassium as well as body pH. The routine status of these analytes would help in the prediction of an individual's health and to manage personalized disease care in times of emergencies.<sup>65</sup> Notably, a wearable sensor should have a quick response time, be cost-effective, be selective, have a repeatable response, and be sensitive. Besides, the sensor should be able to detect multiple analytes or parameters in a real-time manner that will reflect more precise health updates of an individual, since the human body is a complex system where one parameter is associated with more than one disease condition.<sup>66</sup>

However, most available wearable sensors are incapable of detecting and integrating the signals from several analytes. There is a need for multiplexed sensors to monitor glucose, sodium lactate, potassium, and other body metabolites simultaneously in a real-time manner. There is undoubtedly a pressing need to create innovative, multi-analyte detection ability, simple-to-use wearable sensor devices. In this context, a completely integrated wireless multiplexed wearable sensing technology was fabricated by Semionatto *et al.* in 2017 which is capable of monitoring sweat electrolytes and metabolites in a real-time manner.<sup>67</sup> This electrochemical sensor was screen-printed with PET stickers attached to the nose pads on each side of the eyeglasses. The wearable sensor was developed by combining a potentiometric potassium ion-selective electrode and an amperometric lactate biosensor into the two nose-bridge pads of the spectacles and connecting them to an electronic backbone mounted on the arms of the spectacles (Fig. 4IA and IB). This amperometric and potentiometric sensor was printed on two circuit boards (PCBs) mounted on the arms of the eyeglass. The potentiometric and amperometric measurement capabilities of the lactate and potassium sensors, as well as wireless data transfer, were connected to each of the PCBs. This sensor can be connected wirelessly to a host device, such as a smartphone, smartwatch, or laptop, using this controller's built-in Bluetooth low energy (BLE) feature. The lactate eyeglasses biosensor is based on the amperometric monitoring of the hydrogen peroxide product and the lactate oxidase-mediated oxidation of lactate to pyruvate and  $\text{H}_2\text{O}_2$  (Fig. 4(IC)). Fig. 4(ID) shows the construction and functionalization of the lactate biosensor for the

nose-bridge pad. A limit of detection (LOD) of 0.39 mM ( $\text{CLk} = 3$ ) and a linear range of detection up to 10 mM lactate were obtained. Open-circuit potential measurements were used to assess the analytical performance of the potassium sensor, which provides a LOD of  $10^{-3.9}$  M. The lactate and potassium electrodes were each linked to a PCB that was positioned on each of the arms of the eyeglass to form the integrated MAG multiplex device (Fig. 4(IIA)). Using the wireless boards, *in vitro* data calibration curves were produced through an experimental arrangement which is depicted in Fig. 4(IIB). The potassium sensor's potential-time response to an increase in concentration of potassium chloride from 0.01 to 10 mM as shown in Fig. 4(IIC). The response of the lactate sensor while increasing the concentration of lactate from 0 to 10 mM is shown in Fig. 4(IID). Before on-body tests, each sensor was calibrated. During the body test, the sweat's potassium and lactate levels were monitored using a sensor as shown in Fig. 4(IIIa,a') and (IIIb,b'). While exercising, potassium and lactate levels in sweat were detected at the same time, the lactate PCB was repeatedly turned on and off, and simultaneously the potassium level was continuously measured. This ON/OFF process of the lactate sensor caused no interference in the potassium response, suggesting low cross-talk and effective integration of a multiplex wireless sensor into the spectacles. Also, the cross-talk experiment indicates a quick return to the formerly recorded signal and a quick and reliable response. The body glucose level in sweat concerning the time profile is shown in Fig. 4(IIICa,a'). The glucose sensor calibration curve was established by measuring the blood glucose ( $126 \text{ mg dl}^{-1}$ ) using a commercial glucose meter for comparison purposes (Fig. 4(IIIE)). This led to an estimate of the sweat glucose level of 0.2 mM (Fig. 4C), which follows the anticipated sweat-blood glucose association. Wireless signal transduction was demonstrated coupled with sweat lactate and potassium levels measurement simultaneously with no potential cross-talk. Expanding the complete integrated "Lab-on-a-Glass" wireless multiplexed wearable sensor device to simultaneously monitor more sweat electrolytes and metabolites is a simple approach and this system could be further enhanced by adding temperature and pH microsensors integrated with fluidics to regulate the flow of sweat. This non-invasive wearable device can bridge current gaps in wearable sensor platforms, which is needed for continuous health care monitoring and assessable remote diagnostics, and offers an appealing alternative to other sweat-sensing devices.





**Fig. 4** (I) (A) screen-printed interchangeable sticker sensors. (B) Printed MAG eyeglasses combined with a wireless circuit board. (C) Electrochemical sensor on a nose pad with a potassium and lactate sensor associated with recognition and transduction steps. (D) Screen printing process steps for lactate and potassium sensor. (II) (A) MAG device with amperometric and potentiometric PCBs. (B) *In vitro* measurement setup of the device. (C) Potassium sensor response. (D) Lactate sensor response curve. (E) Glucose sensor response curve. Inset: Calibration plot for lactate, potassium, and glucose respectively. (III) (A) Wireless measurement of sweat potassium (a,a') and lactate (b,b') while cycling. (B) Stationary cycling bike with volunteer wearing the MAG device. (C) Measurement of glucose (a,a') and control with no sensor (b,b') during exercise using the device. Adapted with permission from ref. 67. Copyright 2017 Royal Society of Chemistry.

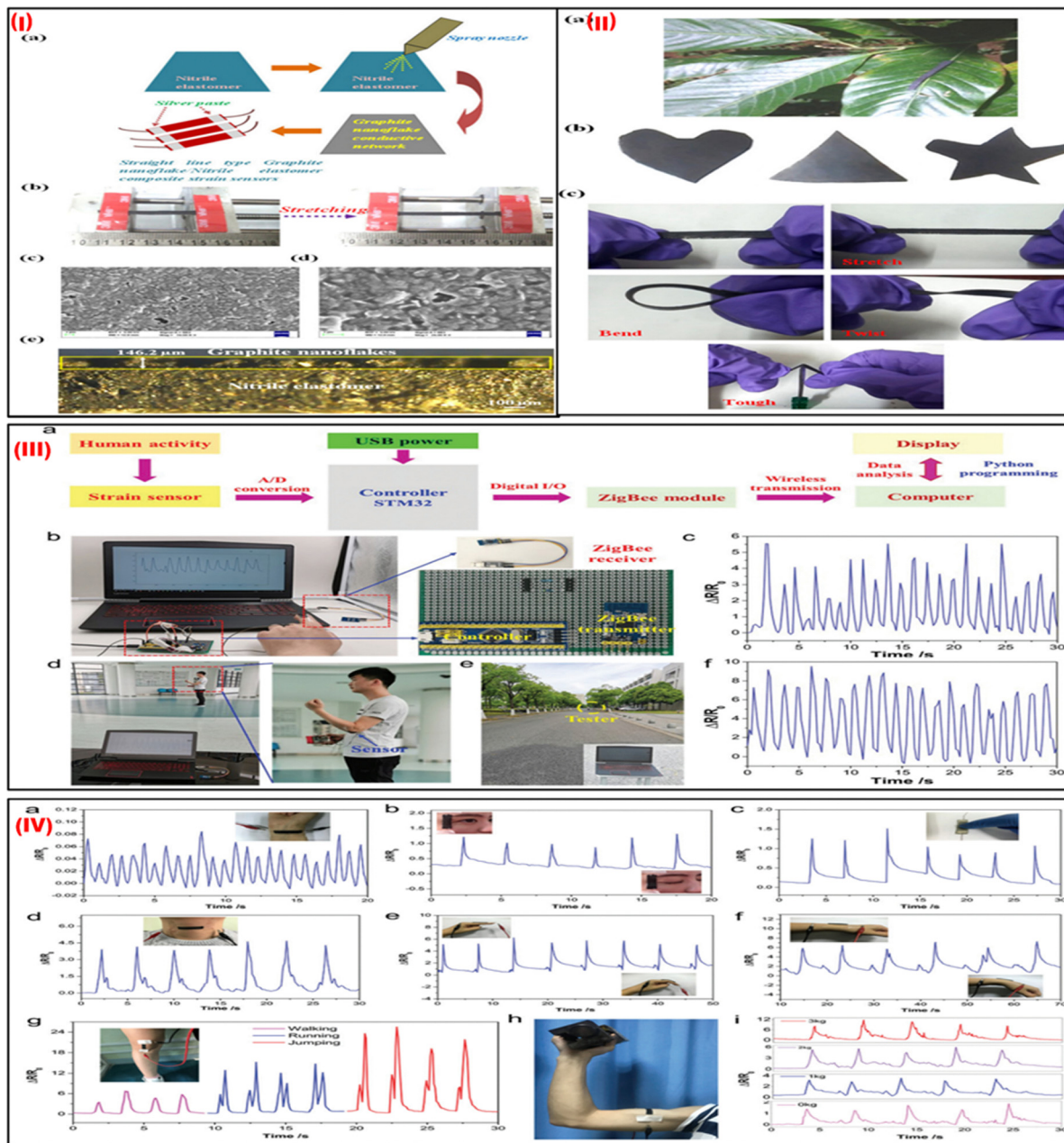
### Wearable strain sensors

Ultrasensitive stretchable strain sensors for human motion detection are currently receiving a lot of attention.<sup>68</sup> In a recent study, spray-coated graphite nanoflakes were used for developing a wearable sensor.<sup>69</sup> This sensor was attached to highly elastic nitrile elastomers. The wearable strain sensor is easy to manufacture and exhibits an ultra-high strain sensitivity much higher than the other available stretchable strain wearable sensors. The development of the graphite nanoflake/nitrile rubber nanocomposite-based wearable sensors is depicted in Fig. 5Ia. The wearable and skin-mountable strain sensors with noticeable stretchability are illustrated in Fig. 5Ib. The SEM picture and cross-section of the graphite nanoflake/nitrile rubber nanocomposite are shown in Fig. 5Ic–e, highlighting its outstanding adhesion characteristics and conspicuous uniformity. By placing the strain sensor on the leaf of a plant,

as shown in Fig. 5IIa, the lightweight quality of the device was demonstrated. For various applications, graphite nanoflake/nitrile elastomer nanocomposites can be easily synthesized in various shapes, such as triangles, hearts, and stars, as shown in Fig. 5IIb. Additionally, the nanocomposites withstand considerable stretching while holding, bending, and twisting, demonstrating their notable flexibility (Fig. 5IIc). The stretchable strain sensors can sense up to 30% strain and exhibit a highly sensitive gauge factor (GF) of  $868.12 \pm 56.90$ , which is noteworthy. The electrical resistance variation, which is a key factor in electromechanical performance, is significantly changed by microstructural percolative network cracks with strain during mechanical distortions. This sensor can be used as an electronic skin for health monitoring applications which helps in monitoring full-range human activity while projecting reversibility, fast response time and recovery speeds







**Fig. 5** (i) (a) The manufacturing procedure for strain sensors made of an ultrasensitive graphite nanoflake/nitrile elastomer composite. (b) The tensile strains revealed the good stretchability of the strain sensor. (c) An SEM picture of the conductive network made up of graphite nanoflakes. (d) A magnified SEM picture of (c). (e) A cross-sectional optical image of the graphite nanoflake/nitrile elastomer nanocomposite strain sensors. (ii) (a) Strain sensors are robust and resilient, and lightweight and can be placed on leaves. (b) Various shapes of a graphite nanoflake/nitrile elastomer nanocomposite. (c) Graphite nanoflake/nitrile elastomer nanocomposite strain sensors are tough and can be stretched, bent, and twisted. Adapted with permission from ref. 69 Copyright 2022 Royal Society of Chemistry. (iii) (a) A setup of the wireless strain sensor. (b) Images of the sensor comprise a portable power source, controller, with a ZigBee receiver, and strain sensor. (c) Signal responses of finger-bending were captured using the sensor system. (d) A tester holding a circuit board and a power source while wearing a sensor on their elbow joint and observing a computer display of electrical signals. (e) A tester who was moving outdoors 50 meters to the ZigBee module. (f) Response signals from the arm bending sensor. (iv) the G/CB/Ni-2 strain sensor monitors motion in a real-time manner. Reaction signals include (a) wrist pulse, (b) blinking, (c) tensing, (d) swallowing, (e) bending of fingers, and (f) wrist movement. A picture of the sensor that is fastened to the wrist shown in insets (b)–(f). Photos of the matching human gestures are included as (g) walking, running, and jumping reaction signals. An image of the sensor mounted over the knee joint is shown in the inset in (g). (h) A picture of a sensor that was fastened to the tester's biceps muscle. (i) Reaction signals when lifting dumbbells of various weights. Adapted with permission from ref. 70 Copyright 2020 Royal Society of Chemistry.

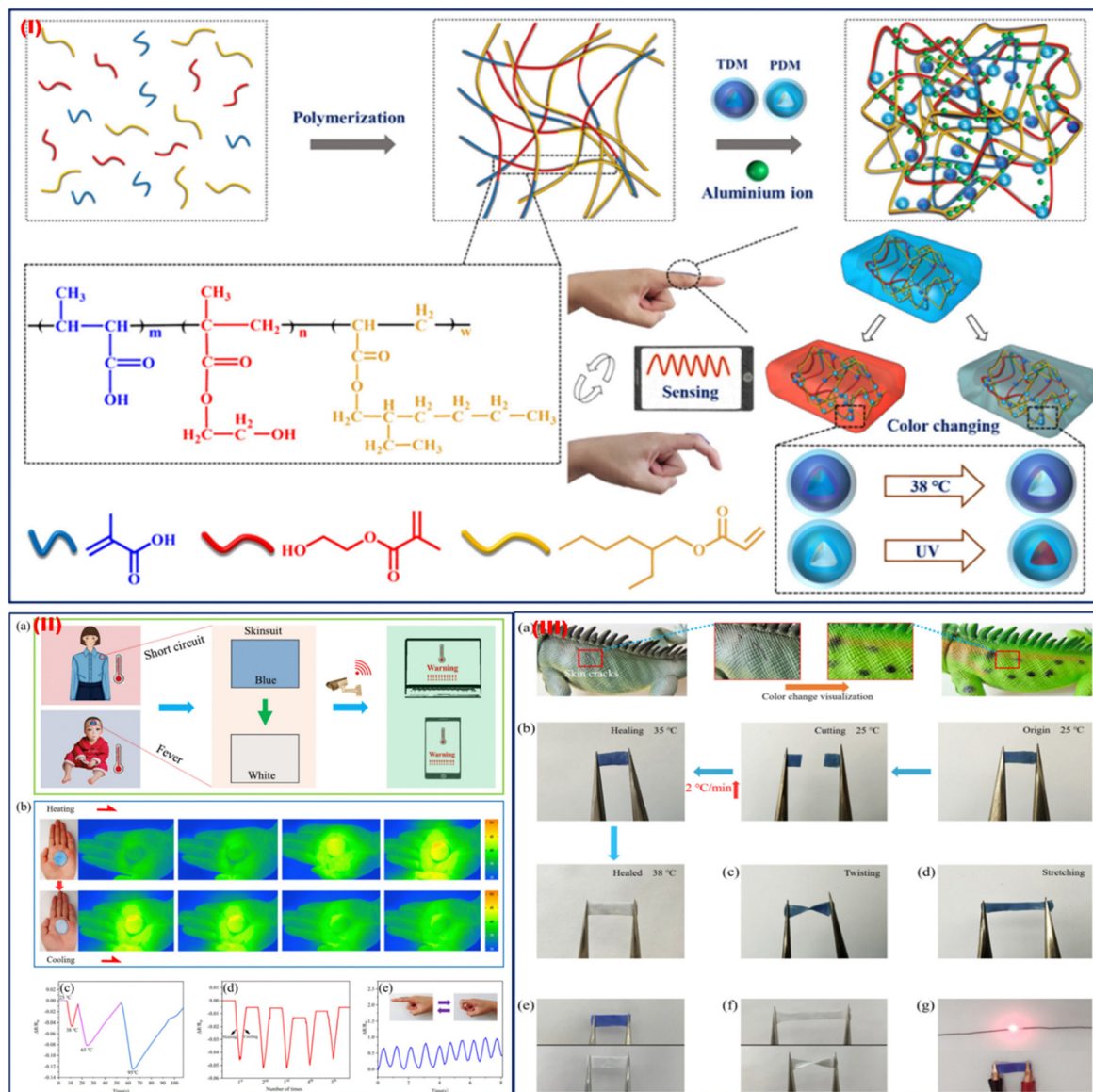
(7.5 ms and 5 ms, respectively), and admirable robustness. This sensor can be employed for human activity monitoring

in healthcare diagnostics, soft robotics, and other biomedical applications.







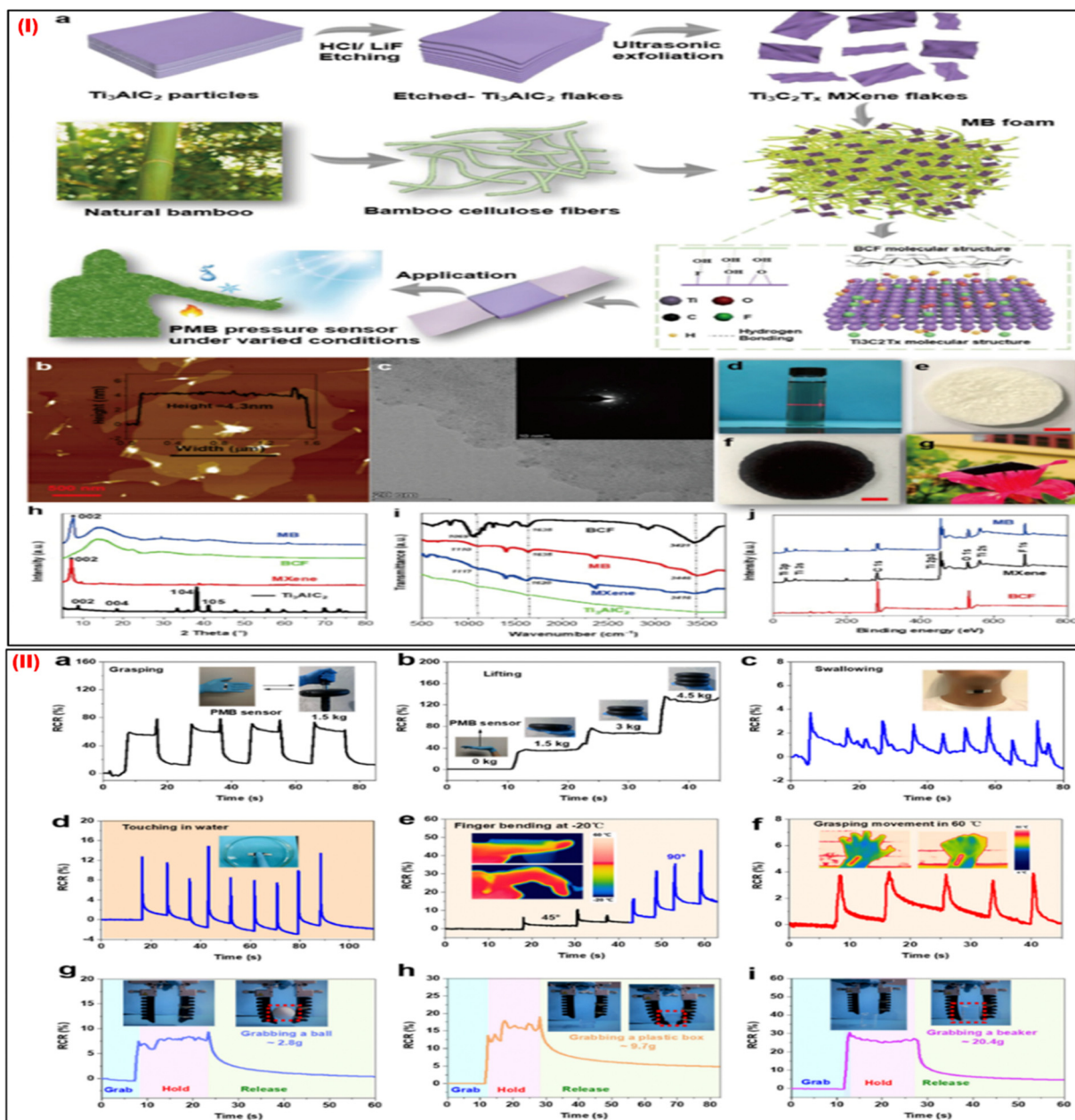


**Fig. 6** (I) Illustration of the TDM/PDM/polyacrylate hybrid hydrogel preparation process. (II) Early warning system to track the human temperature. (b) Thermal images were captured using an infrared thermal camera while the hybrid hydrogel was being heated. (c) The hybrid hydrogel's resistance change ratio ( $DR/R_0$ ) at 25, 38, 65, and 95 °C. (d) During heating and chilling cycles, the resistance change ratio ( $\Delta R/R_0$ ) of the TDM/PDM/polyacrylate hybrid hydrogel. (e) The hybrid hydrogel's sensing capabilities at 38 °C. (III) (a) Chameleons in various forms mending their discolored damaged skin. (b) The hybrid hydrogel's visible self-healing mechanism. (c) and (d) Properties of the repaired hybrid hydrogel in terms of twisting and stretching. (e) The hybrid hydrogel's stain-resistance characteristics. (f) The hybrid hydrogel's stretching and twisting characteristics following repair. (g) A picture of the fixed TCP/PCP/polyacrylate hybrid hydrogel shining an LED bulb. Adapted with permission from ref. 71 Copyright 2023 Royal Society of Chemistry.

sensor demonstrates great pressure sensing capability, good biocompatibility, and noteworthy work trustworthiness to resist temperature variation, moisture/water, and UV irradiation—in stark contrast to earlier MXene composite-based pressure sensors (Fig. 8II(a)–(i)). Furthermore, to demonstrate the PMB pressure sensor's enormous potential for robotic tactile sense, it was also efficaciously combined with soft robotic hands. A soft robotic gripper hand equipped with the PMB pressure wearable sensor was used to grab several things of varying weights, including a beaker, a plastic box, and a table tennis

ball. Various human actions under normal and challenging environmental conditions can also be monitored using a PMB pressure sensor. Beyond their present uses, wearable pressure sensors have a bright future ahead. Improvements in these devices could result in better medical diagnostics, such as tracking cardiovascular health or anticipating respiratory problems. These sensors could improve performance analysis in sports. Furthermore, integrating AI with IoT could transform sectors like ergonomics, fitness, and healthcare by promoting a more responsive and connected world.





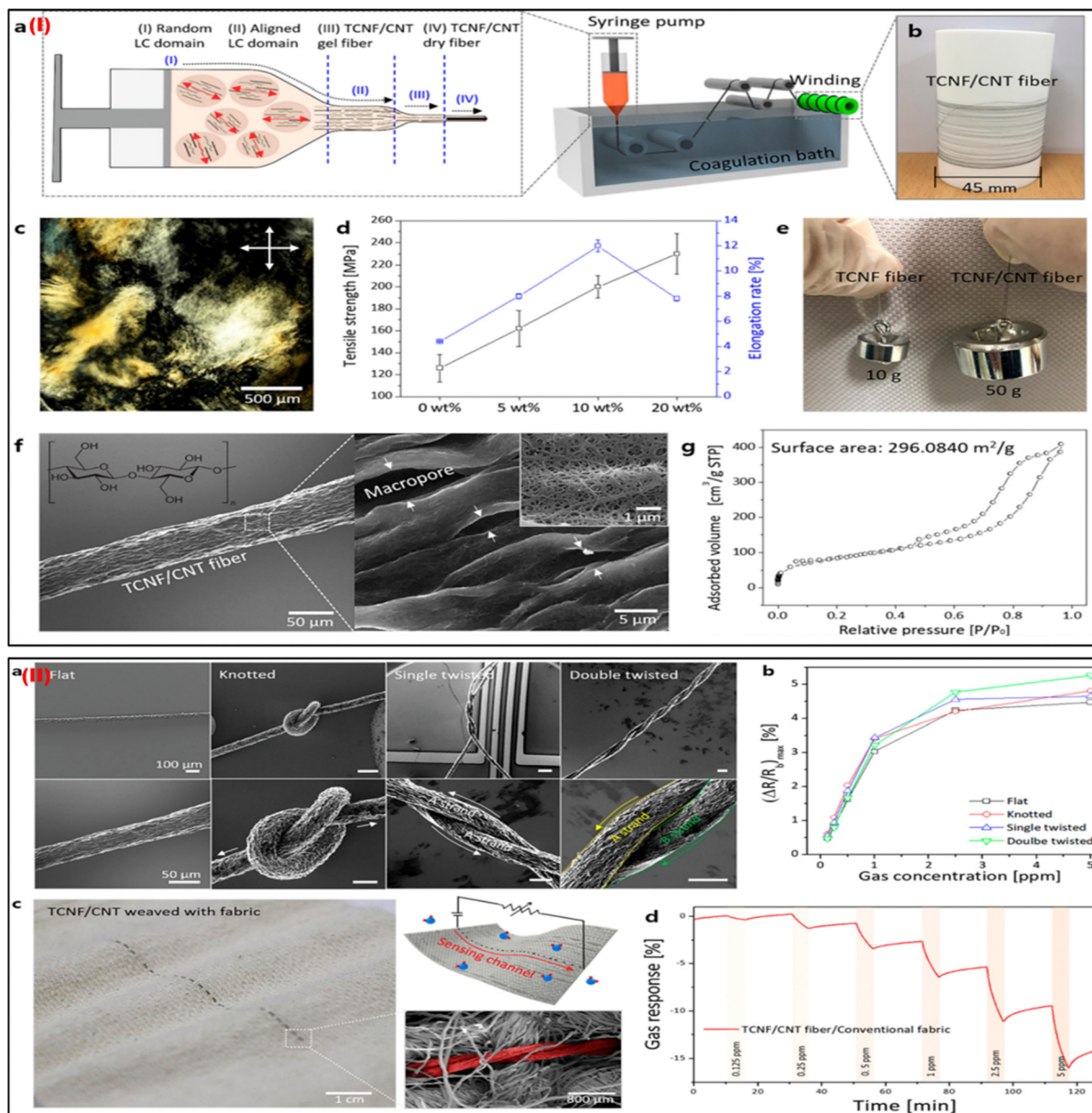
**Fig. 7** (I) (a) Steps of fabrication of PMB pressure wearables. (b) Images of the MXene nanosheets taken with an AFM and (c) TEM images; the inset displays the SAED pattern. (d) The MXene solution, (e) the BCF foam, (f) the MB foam, and (g) the MB foam on a flower. (h) The XRD spectra of  $\text{Ti}_3\text{AlC}_2$  powders, MXene nanosheets, BCF foam, and MB foam, and (i) FTIR. (j) MXene nanosheets, MB foam, and BCF XPS spectra. (II) The use of the PMB pressure sensor in soft robotics and the sensing of human movement. RCR responses of the sensors to detect significant motions such as (a) gripping and (b) lifting heavy objects. (c) RCR sensor responses are used to track minute movements. RCR sensor responses in challenging conditions, such as (d) detecting finger touches in water, (e) observing finger bending at a low temperature of  $20\text{ }^\circ\text{C}$ , and (f) sensing gripping motion at a high temperature of  $60\text{ }^\circ\text{C}$ . Adapted with permission from ref. 72. Copyright 2022 American Chemical Society.

Integrating carbon nanotubes (CNTs) into nano cellulose enabled Cho *et al.* (2019) to mass-produce sensing fibers with high mechanical qualities and sensing capabilities without requiring extra effort.<sup>73</sup> To facilitate liquid-crystal characteristics, nano cellulose obtained from tunicate (TCNF) was homogeneously mixed with single-walled CNTs. Composite fibers (TCNF/CNT) are continuously created by wet spinning in aligned directions. The TCNF/CNT can be adequately

concentrated during the LC phase to use the common wet-spinning method for constant fiber synthesis (Fig. 8Ia). The mechanical characteristics of the TCNF/CNT fiber, the weights lifted by single fibers, the TCNF/CNT image, the polarized optical microscopic image, the SEM image, and the isothermal adsorption/desorption plot are shown in Fig. 8Ib–g. As shown by SEM pictures and the time-dependent  $\text{NO}_2$  sensing response of the intertwined TCNF/CNT fiber, TCNF/CNT fibers have high







**Fig. 8** (I) Characterizations of the TCNF/CNT fibers and their scalable production. (a) Diagrams for the hybrid LC spinning technique-based continuous manufacture of TCNF/CNT fiber. (b) Picture of the bobbin-collected TCNF/CNT (20) fiber. (c) The image shows the hybrid schlieren LC texture of TCNF/CNT (20) at 30 mg mL<sup>-1</sup> taken with polarised optical microscopy (POM). (d) The relationship between the TCNF/CNT fiber's mechanical characteristics and the CNT content. (e) A picture of the weights that the single fibers were able to lift. (f) TCNF/CNT (20) fiber SEM pictures at low and high magnifications. (g) The TCNF/CNT (20) fiber's isothermal adsorption/desorption plot and BET surface area. (II) TCNF/CNT fibers have good mechanical flexibility, making them ideal for wearable sensors. (a) SEM pictures of the TCNF/CNT (20) fibers that have been merged with sensing apparatus in knotted, flat, single-, and double-twisted forms. (b) The maximum  $(\Delta R/R_0)$  of the flat, knotted, single- and double-twisted TCNF/CNT (20) wearable sensors in the NO<sub>2</sub> concentration range of 0.125–5 ppm. (c) Images of a TCNF/CNT fiber woven into standard fabrics, including photos, schematics, and SEM pictures. (d) The woven TCNF/CNT fiber's real-time NO<sub>2</sub>-sensing performance with common wearable textiles. Adapted with permission from ref. 73. Copyright 2019 American Chemical Society.

mechanical flexibilities and good sensing abilities as wearable sensors (Fig. 8IIa–d). Excellent gas (NO<sub>2</sub>) sensing efficiency with great selectivity and high sensitivity is confirmed by the TCNF/CNT fibers. The TCNF/CNT fibers can also withstand difficult distortions while preserving their inherent sensing qualities, and they can be seamlessly incorporated with traditional fabrics utilizing a direct weaving process. The ability to run

this wearable sensor fiber manufacturing approach at extremely low process costs is also advantageous. For the manufacturing of one meter of TCNF/CNT fiber, the process cost of synthesis is around 0.00403 \$ per meter. This scalable, meter-scale production of functional composite fibers is anticipated to offer a framework for the mass manufacture of adaptable wearable sensors.

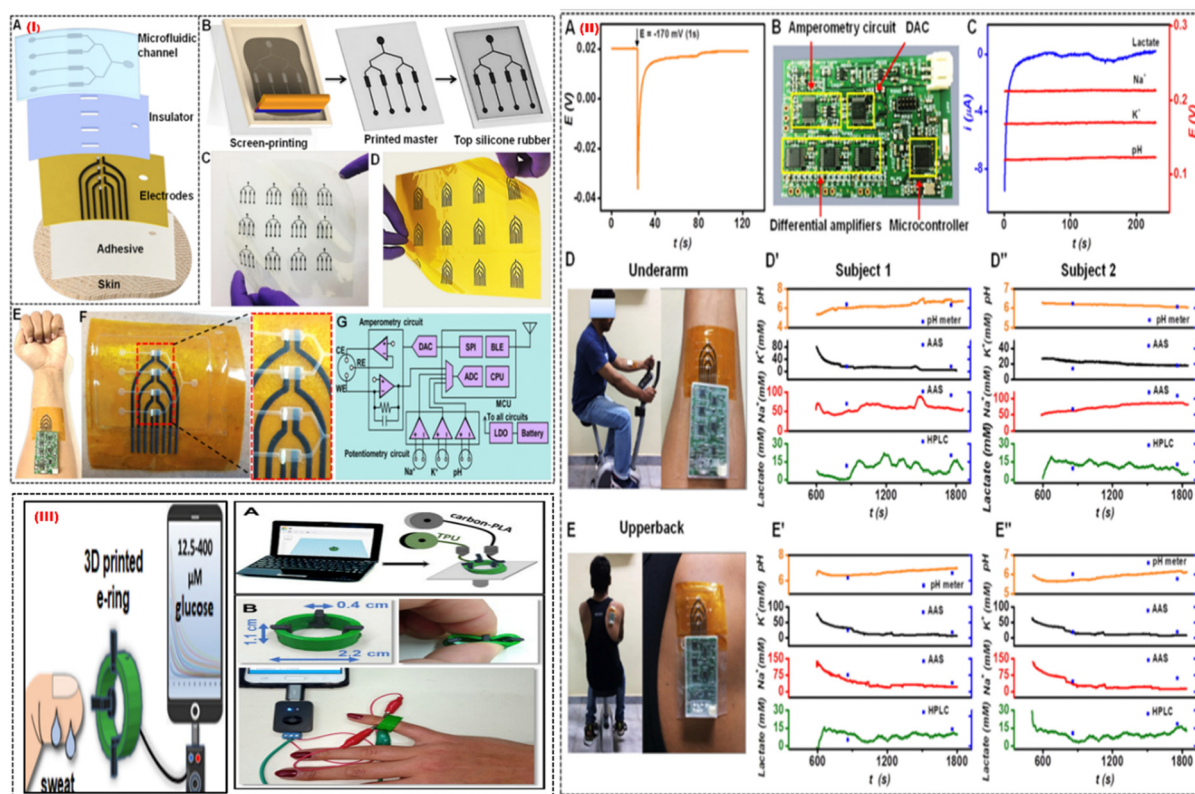


## 5. Microfluidic-based platform for multiplexed integrated wearable sensors

Recently, novel microfluidics approaches have sparked the development of miniature devices that can be employed for carrying out a variety of tasks, including the trapping of particles and cells, size-based segregation of particles and cells, the production of nanomaterials, the formation of droplets, and testing of drugs.<sup>74</sup> Sample collection, treatment, and analysis have all been carried out using soft microfluidic technology. These tools are used to monitor electrolyte loss and compositions while also measuring biomarkers in real-time. Numerous applications in the field of diagnostics, such as food quality testing, environmental monitoring, and health diagnostics, have employed paper-based microfluidic analytical devices. However, most of these platforms are unusable and unfit for continuous monitoring applications. Moreover, flexible microfluidic patches are fabricated using traditional

photolithographic procedures, which are costly and time-consuming and obstruct the mass manufacturing of electrochemical multianalyte sensing.

Real-time continuous sweat biomarker investigations are a prerequisite for health care and for this purpose the development of cost-effective microfluidic devices with quick sample collection and multiplexed analyte identification capabilities is crucial.<sup>75</sup> Vinoth *et al.* (2021) recently fabricated a printed microfluidic-based wearable device for multiplexed high-throughput electrochemical analysis of sweat samples.<sup>76</sup> For this, an array of electrodes printed over a flexible polyimide layer and an insulator film to create leakage-free closed, fluid paths to direct sweat samples to the sensing electrodes allows for the one-step production of numerous identical patterns on affordable substrates (Fig. 9(IA)). The fabrication of roll-to-roll several uniform patterns using the screen-printing technique is used to create a carbon-based master mould. After the carbon ink is generated using a thermoplastic elastomer called SBS binder, it is screen-printed with the appropriate fluidic channel



**Fig. 9** (I) Process of a printed microfluidic device. (A) The microfluidic patch's several layers, and (B) the silicone rubber-based microfluidic channels from the screen-printed carbon master is shown schematically. (C) The optical pictures display a variety of printed carbon masters and (D) multiarray electrodes. (E) Pictures of a skin-interfaced, completely integrated microfluidic sensor and (F) a multiarray electrode with four sensing chambers in close-up. (G) Diagram of the design of a tiny PCB with multiplexed analysis and wireless mode of data transmission capabilities. (II) Analysing sweat on the body. (A) The OCP responses for Na-ISE are shown when a nearby amperometric sensor is subjected to a constant voltage of about 170 mV for one second. (B) An optical picture of the portable circuit board. (C) Using the tiny circuit board, measurements of the potentiometric and amperometric responses are simultaneous. (D) Optical pictures displaying the integrated microfluidic wearable sensor on the underarm and (E) upper back areas. For two participants, multiplexed sensor responses were recorded in the (D', D'') underarm and (E', E'') upper back regions. Adapted with permission from ref. 76. Copyright 2021 American Chemical Society. (III) (A) The stages involved in making the 3D-printed e-ring. (B) Images of the 3D-printed e-ring that display its flexibility, dimensions, and connection to the mobile and small potentiostat. Adapted with permission from ref. 77. Copyright 2021 American Chemical Society.







watch gave a read-out corresponding to the analyte concentration. The same group recently reported the development of a flexible wearable bioelectronic system to monitor the analytes during wound healing and release drugs to the infected wound.<sup>78</sup> The multiplexed sensor was developed for uric acid, lactate, glucose, ammonium, pH, and temperature sensing.

The microneedle-based wearable sensor is another wearable platform for the continuous monitoring of biomarkers in the interstitial fluid.<sup>79</sup> Since it samples the bio-fluid inside the

body, it gives a more detailed account of the biomarkers of interest.<sup>80</sup> Tehrani *et al.*, demonstrated the development of a wearable microneedle-based sensor for the sensing of glucose, lactate, and alcohol content in the interstitial fluid.<sup>81</sup> Continuous monitoring of these biomarkers is of significant interest since these are related to various illnesses. Fig. 10I shows the developed wearable sensor along with the exploded view of the sensor construction. The sensor construction shows the presence of three working electrodes. The electrodes were

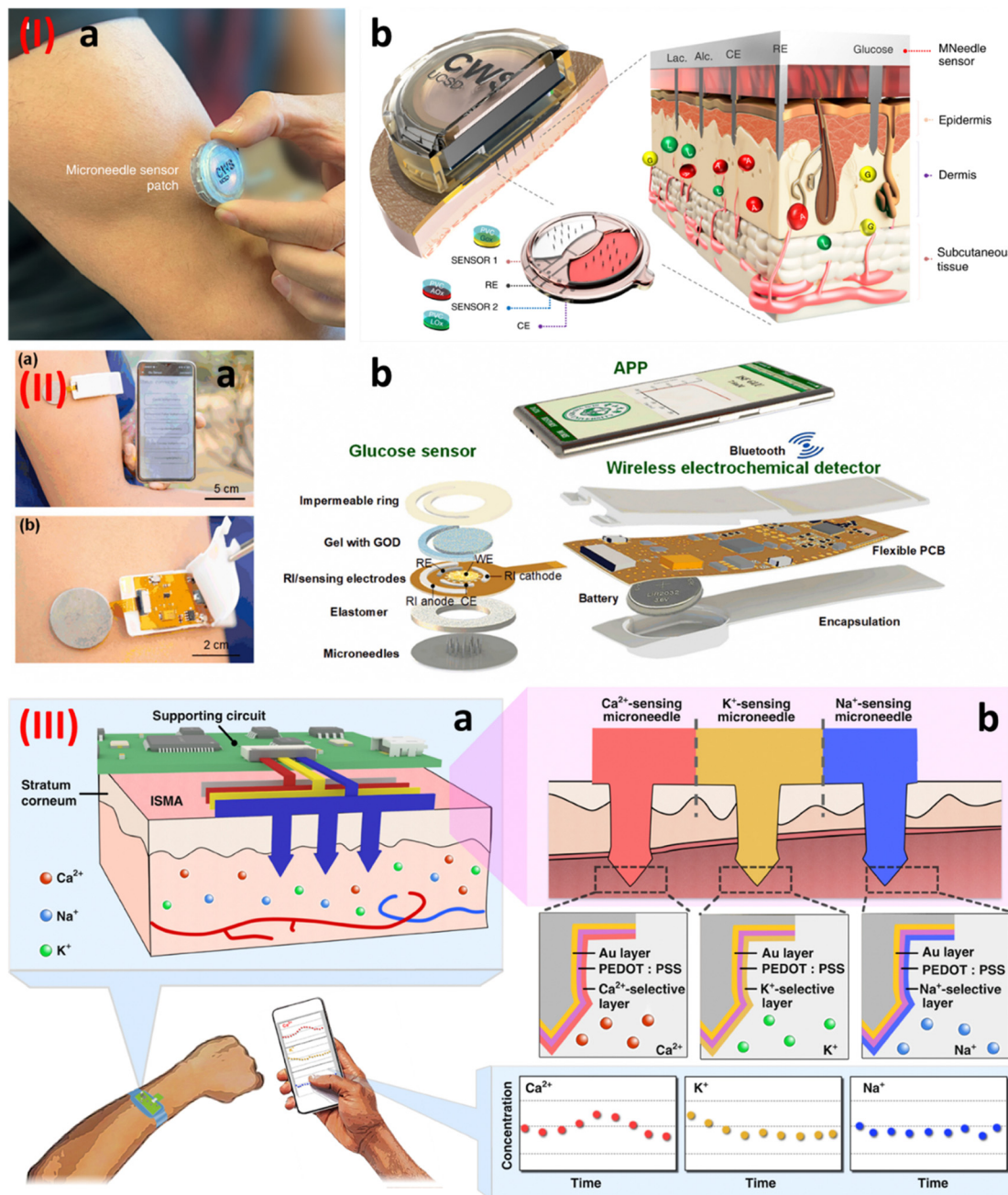


Fig. 10 (I) (a) A wearable integrated microneedle-based sensor, and (b) an enlarged view of the sensor construction.<sup>81</sup> Copyright 2022 Nature Biomedical Engineering. (II) (a) An integrated microneedle-based sensor transmitting data wirelessly, and (b) an enlarged view of the various components of the wearable sensor.<sup>82</sup> Copyright 2022 Elsevier. (III) (a) and (b) A stainless steel-based microneedle patch for the simultaneous detection of calcium, potassium, and sodium ions.<sup>83</sup> Copyright 2023 Nature.



modified with glucose oxidase, lactate oxidase, and alcohol oxidase. The *in vivo* testing of the sensor showed its sensing performance during cycling, eating, and drinking. Cheng *et al.*, reported the development of a touch-based and wearable microneedle-based glucose sensor.<sup>82</sup> The authors in this work tried to address the issue of low flux and inconsistency during the reverse iontophoresis approach that is generally used for glucose sensing. The authors proposed using a microneedles-based skin penetration system, which was then used for the reverse iontophoresis-based extraction. The authors showed that this system improved the glucose extraction flux by 1.6 times. Fig. 10II(a) and (b) show the sensor construction. The sensor shows the presence of microneedles for the sample extraction. The electrodes were modified with glucose oxidase for glucose sensing and the data generated was transmitted wirelessly to a smartphone. The determination of ions also helps in the determination of various illnesses in the human body. In this regard, Huang *et al.* developed a stainless steel-based microneedle patch for the simultaneous sensing of calcium, potassium, and sodium ions.<sup>83</sup> The stainless-steel microneedles were modified differently for the detection of different ions as shown in Fig. 10III(a) and (b). A layer of gold was first deposited electrochemically on the microneedles, followed by the deposition of PEDOT:PSS polymer. These microneedles were then modified with calcium, potassium, and sodium selective membranes for the detection of calcium, potassium, and sodium respectively.

### Multifunctional flexible sensors

Wearable technology relies on multifunctional flexible sensors, which can be used for various purposes, including health monitoring, motion and activity tracking, environmental and contextual sensing, human-machine interfaces, pain management and rehabilitation, agriculture and sports, sports performance monitoring, and wearable energy harvesting. The long-term monitoring of physiological parameters with precise pulse monitoring could provide much information non-invasively, which demands a versatile pressure sensor with high sensitivity over a wide linear range (up to 10 kPa). Still, the combination of linearity region and sensitivity could be challenging. He *et al.* in 2019 demonstrated a highly conductive inter-facially self-assembled graphene-based high-sensitivity and high-accuracy wearable pulse monitoring system. The authors showed highly accurate pulse signal monitoring in real time, even during exercise with high sensitivity (1875.53 kPa<sup>-1</sup>) and a wide linear detection range (0–40 kPa).<sup>84</sup> Next-generation high-performance flexible or wearable electronics rely on flexible human-machine interfaces, which require high-performance novel materials, augmented structures, and design methodologies. A metal oxide (zinc oxide) based on a flexible acoustic platform has been demoted by Zhang *et al.* in 2022 and could be utilized in a wide range of applications, including as a loudspeaker, a microphone, or an ambient sensor based on its excitation frequencies. The authors exhibited respiratory monitoring using their zinc oxide-based flexible sensor with a high-temperature coefficient of frequency of  $-289 \text{ ppm K}^{-1}$ .<sup>85</sup> The future bioelectronics for accurately monitoring human

physiological health requires integrated flexible and stretchable multifunctional sensors. Many challenges remain, including the crosstalk among the integrated multifunctional sensors into a common substrate intended for the simultaneous monitoring of health. Zhang *et al.* in 2022 demonstrated multifunctional sensors integrated into a stretchable substrate for the real-time measurement of strain, temperature, and ECG without interfering with each other. In-situ polymerization self-assembly of 3,4-ethylenedioxythiophene (EDOT) on MXene-Ti<sub>3</sub>C<sub>2</sub>T<sub>x</sub> was achieved in an aqueous solution in the absence of an oxidant to develop a single composite material. The composite material showed high strain sensitivity (2075; >22% strain), a good temperature coefficient of resistance (0.52% K<sup>-1</sup>), and a low skin-electrode impedance (51.08 kΩ at 10 Hz). No oxidant and facile transfer of functional materials into thermoplastic elastomer (ultrathin and stretchable) makes this method more feasible for fabricating high-performance multifunctional sensors.<sup>86</sup> A sensor with a stable electrical output is highly desired for developing next-generation wearable health monitors. Zhu *et al.* in 2018 reported stretchable carbon nanotube transistor-based robust temperature sensors by adopting circuit design strategies. Inaccuracy, strain-dependent errors, and sensor calibration of any sensor are the major challenges. However, the authors reported inaccuracy of only  $\pm 1 \text{ }^\circ\text{C}$  within a uniaxial strain range of 0–60% by employing the static and dynamic differential readout techniques.<sup>87</sup>

### Implantable sensors

Implantable sensors are biomedical devices capable of providing continuous biomarker information once implanted in the human body.<sup>88</sup> These devices provide wireless, real-time, and continuous data without the need for repeated surgical interventions.<sup>89,90</sup> The most important biomarker that is of significant interest to clinicians and researchers is glucose and hence, a lot of research has been conducted for continuous glucose monitoring systems. Kim *et al.* in 2022 developed an electromagnetic biosensor for continuous glucose monitoring, which was subcutaneously implanted. The sensor was able to track the changing dielectric permittivity as the blood glucose levels changed. The authors demonstrated the sensors working in swine and beagle through intravenous glucose tolerance tests.<sup>91</sup> Another example of an application of an implantable sensor is for tactile pressure sensing. Here the sensing system is implanted subdermally, which was demonstrated by Du *et al.* in 2023. The sensing system was based on a capacitive pressure sensor, which was supported by other electronic parts. The sensor was tested by implanting it in the fingertip and was capable of measuring the skin forces at a resolution of 4.3 mN.<sup>92</sup> Having mentioned a few examples of implantable sensors, it is important to mention one of the key challenges associated with them. Since these devices provide continuous and real-time data wirelessly, they require significant power consumption,<sup>93</sup> and hence, research is ongoing for self-powered biosensing systems.<sup>94</sup>

The development of goods that are simple to incorporate into a person's lifestyle is necessary for wearable sensor



Table 1 List of commercially available wearable sensors along with their price and market availability

S. No	Product name	Company	Analyte, Sample	Wearable Platform	Monitoring Technique	Price	FDA Approval	Ref.
1	Lingo sensor	Abbott	Track both glucose and ketone, lactate, and alcohol levels	Skin	Optical colorimetry	\$420	Yes	98
2	Biosensor BX100	Philips	Deterioration detection solution	Patch	Image-guided therapy		Yes	99
3	Lifetemp	Isansys lifecare	Body temperature	Armpit	Silicone gel adhesive			100
4	Paediatric sensors	Isansys lifecare	Heart rate, pulse rate and respiratory rate	Patches	Remote accessibility			100
5	3150 WristOx	Isansys lifecare	Robustness and reliability	Wrist-worn	PPG waveform	\$739		100
6	Sensit smart	PalmSens	Capable of EIS up to 200 kHz	Skin	Screen printed electrodes			101
8	Fitbit smart watch	Fitbit <i>versa</i>	Heart rate monitor	Wrist watch	Electrochemical device	\$179.95	Yes	102
9	Fingertip SpO <sub>2</sub> sensor AMD-DS-NM0002-4	Amydi-med Electronics	SpO <sub>2</sub> sensor	Fingertip, multi-position, foot, toe	Transflectance, reflectance	\$3	Yes	103
10	Vios chest sensor	Vios	ECG, heart rate, respiratory rate, SpO <sub>2</sub> , pulse rate, posture, and activity	Chest	Medico electrode		Yes	104

technology to gain widespread acceptance. Sweat analysis has been carried out using most wearable chemical sensors in conjunction with flexible, durable, temporary tattoo-like devices, skin patches, headbands, spectacles, or wristbands. Recent research has also investigated smart bandages for wound healing, mouthguards, diagnostic devices for saliva monitoring, and eyeglasses, and contact lenses for tear assays as additional devices and accessories for human body biomarker sensing applications.<sup>95</sup> Sensors integrated into the textiles allow for efficient sweat collection and can present unique opportunities for real-time biomarker monitoring.<sup>96</sup> These not only provide a platform for sensing analytes but can also be used for the generation of human motion-induced triboelectric charges, which in turn block microbes.<sup>97</sup> Combining the strengths of the fashion trend and wearable sensors to create wearable fashion accessories will result in a wider adoption of wearable sensor technology that can urgently address the need for disease diagnostics and real-time health monitoring. Some of the commercially available wearable sensors are listed in Table 1.

## 6. Challenges and future scope

Wearable sensor development and commercialization encounter several difficulties. The precision and dependability of sensors are essential for obtaining useful data. First, sensor performance may be impacted by elements like motion artifacts and ambient factors, necessitating rigorous calibration and testing. Second, integration and miniaturization represent significant obstacles. Wearable sensors must be functional while remaining small and unobtrusive. It is technically difficult to balance power usage, computational power, and data transfer in a small area. Third, for wearable sensors, power management is crucial. This is a challenging undertaking that calls for effective power management strategies and low-power components to maximize battery life while satisfying the power

requirements of sensors, CPUs, and wireless connectivity. Moreover, data analysis and interpretation present difficulties. It is essential to create algorithms that can handle and analyse enormous amounts of sensor data and extract valuable insights. Accuracy, miniaturization, power management, data analytics, and user experience will all see advancements as a result of ongoing research and development. Wearable sensors can revolutionize personalized healthcare and promote greater well-being by overcoming these difficulties. Devices like smart-watches and fitness trackers enable sensors to monitor blood pressure, body temperature, blood glucose levels, heart rate, activity levels, sleep patterns, and blood pressure and have revolutionized the field of diagnostics (Fig. 11).

## 7. Conclusion

Keeping up with the fast pace of life is significantly taking a toll on people's health. Access to affordable healthcare for all is also a bottleneck to improving the health of the population. Wearable sensors are a promising candidate to solve this critical issue. These sensors can detect biomarkers and metabolites of interest non-invasively in sweat, saliva, and tears. Though promising, the mass availability of these sensors is still very far from reality. The main reasons are cost, comfort levels, and a lack of integrated systems. This review highlighted the recent efforts in the development of complete integrated prototypes. In a typical integrated system, the sensors, powering system, electronics, and communication systems are packaged tightly in a compact manner, which can be comforting and can be worn by the user without any issue. In this review, we have discussed various physio-chemical sensors, which have the potential for healthcare improvement. We also delved into wearable strain, pressure, thermal, and multifunctional flexible sensors. The challenges being faced while designing and scaling up these sensors are also discussed. This review will be





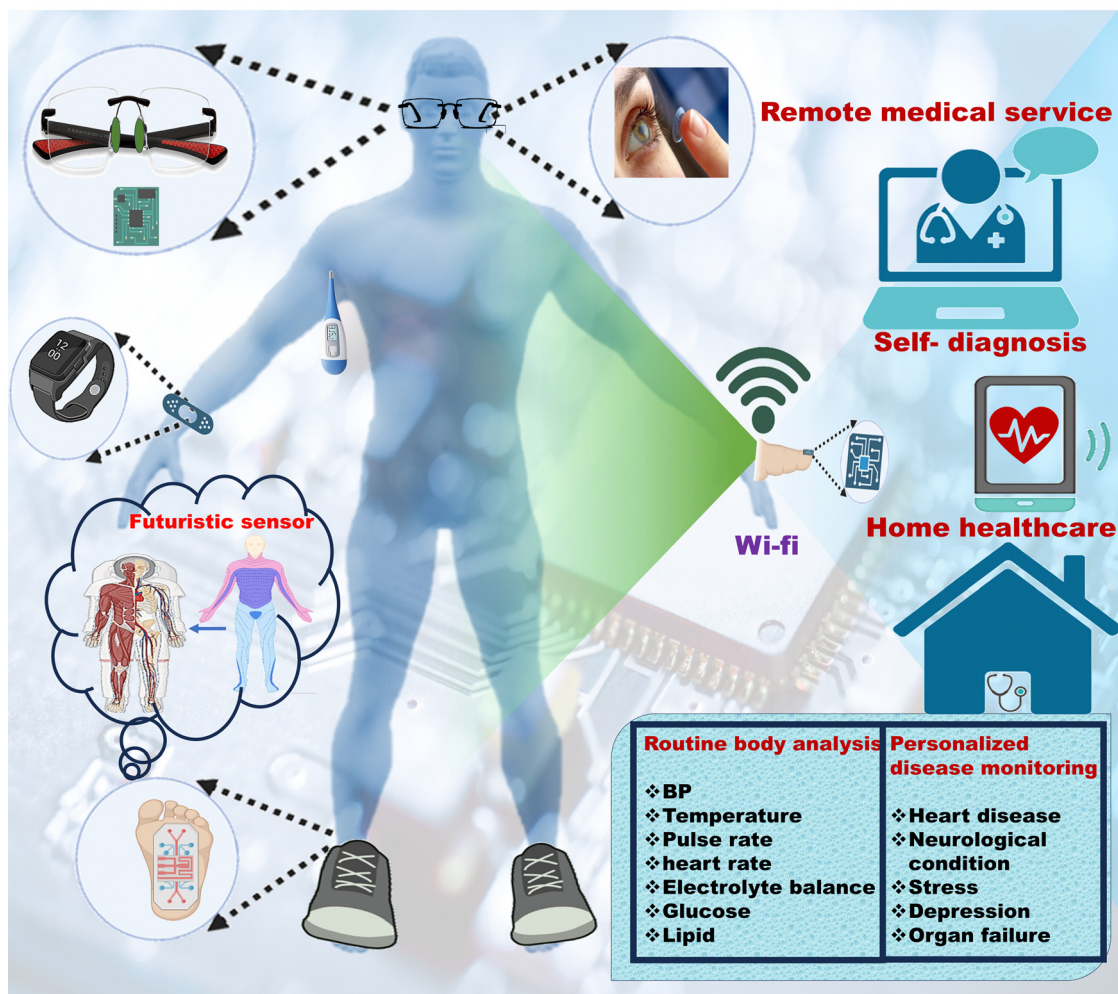


Fig. 11 Futuristic applications of integrated wearable sensors in personalized healthcare [Figure created using icons from Biorender and MS Office].

helpful in the design and development of novel integrated wearable sensors which are expected to start a new era in the field of personalized healthcare.

## Conflicts of interest

The authors do not have any conflicts of interest to declare.

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