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Review Article

Flexible, wearable biosensors for digital health

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ABSTRACT

Flexible and stretchable biosensors have the advantage of enhanced signal validity and patient comfort during physiological signal sensing and biomolecular analysis, crucial for disease diagnosis, treatment and health management. Their lightness, softness and excellent mechanical properties enable effective skin-device interface coupling and skin safety profiles, realizing multi-functional, intelligent real-time sensing. In this review, the basic sensing principles of biosensor systems and their applications are discussed. Moreover, the potential applications and prospective progress of these biosensors are further prospected. Flexible, wearable biosensors have the potential to realize continuous and long-term health monitoring in clinical and daily health care.

1. Introduction

The human body is a complex biological system, exhibiting a myriad of changing physiological signals that reflect the ongoing physiological processes within the body [1–3]. The detection and quantification of such real-time biochemical and biophysical signals with body-integrated sensors provide key opportunities for the advancement of health care [4–7]. At present, however, most clinically available monitoring systems rely on bulky, heavy-weighted equipment, rendering long-term, real-time monitorings of patient health status difficult, especially in out-patient settings [8–10]. Recently, a new class of wearable skin-integrated sensors with the characteristics of lightness, flexibility and portability have found powerful applications in the detection and diagnosis of real-time, continuous physiological states [11]. The capability of such wearable biosensors have expanded from detecting common physical signals, such as temperature [12,13], to more specific biochemical biomarkers, such as blood glucose for diabetes monitoring [14]. Furthermore, these wearable sensors offer the ability to provide real-time digital data that can be recorded by cell phones or tablets, creating breakthrough opportunities for personalized, degitalized medicine [15–18].

Wearable technologies have been empowered by the ability to sample body fluids in a non-invasive manner. These body fluids, including sweat, tears and saliva, may be obtained without damaging the outermost stratum corneum, the protective layer of human skin [19,20]. As a result, sensors based on the analyses of such body fluids are generally more user-friendly due to the advantage of low injury and infection risks

[21–23]. A wide range of applications have been enabled by such non-invasive wearable sensors, including: (1) the detection of biochemical biomarkers for the diagnosis and treatment monitoring of diseases, such as diabetes [24], cystic fibrosis [25], dermatitis [26,27] and peripheral blood vessels disease [28]; (2) the monitoring of physical signals such as heart rate and physical activity; (3) the integration with human-machine interfaces to help patients with speech and movement disorders [29,30]. Moreover, sensors of mechanical flexibility and stretchability that match human skin for mechanical compatibility have demonstrated excellent compliance with skin curvatures and body movements, providing an additional layer of patient comfort, skin safety, and signal accuracy [31–37]. Although wearable technology has made rapid progress in the past few years and several recent reviews have emphasized the attractiveness of modern wearable chemical and physical sensors and related research progress [38–42], our understanding of how wearable technology can fundamentally impact personalized health management has just begun.

In this review, we summarize the powerful functions of skin-integrated electronic products from the perspective of intelligent sensing, embodied in the versatility of skin-integrated sensors for medical care monitoring. We discuss the basic detection principles of current biosensor systems. In particular, we outline the main developments of wearable biosensors that have reached human clinical studies in the past three years to demonstrate their capabilities in biomedical sensing and daily activity tracking. Finally, we discuss future research priorities and commercialization prospects of this exciting, impactful field.

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2. Monitoring mechanisms of biosensors

Fig. 1 classifies current wearable biosensors based on their sensing mechanism: optoelectronics [43–45], ultrasound [46], pressure [47,48], electrochemistry [49], magnetic field [50], and temperature [51]. Upon analyte contact, these sensing components convert their change in energy into electrical signals [52]. Physiological signals, such as temperature [53], pulse [54], glucose [55] and heart rate [56], can be quantitatively determined by this process. This section summarizes key sensing mechanisms utilized in wearable biosensors.

Optoelectronic sensors utilize the change in optical properties based on the interactions between the biometric elements (e.g., hemoglobin) and the target analyte (e.g., oxygen), including changes in absorption, fluorescence, reflectance, emission or interference patterns [57,58]. Namely, optical biosensors gather analyte information via photons. Photodetectors quantify the changes in the concentration or conformation of molecules [59], and then convert them into electrical signals, providing the ability to detect key vital signs such as heart rate, respiration rate, and blood oxygen [60,61].

Pressure-sensitive sensors have been used to measure heart rate, blood pressure and other mechanical variations [62]. They are typically composed of an intermediate conductor sealed with a deformable support matrix [63]. Pressure-sensitive sensors can be classified into capacitive, piezoelectric and piezoresistive based on the sensing mechanism [64]. A capacitive pressure sensor typically composes of a dielectric layer between a pair of parallel electrodes [65]; upon exposure to external force, the change in dielectric constant is harvested to detect the physiological signals of interest [66]. On the other hand, piezoelectric-based sensors utilize piezoelectric materials to convert mechanical deformation into electrical signals [67–70], while piezoresistive pressure sensors use the change in electrical resistance of a material upon mechanical deformation [71].

Human body fluids such as sweat are rich in biochemical substances, the detection of which may unveil key personal health information [72]. Recent progress in wearable sweat sensor development have made clinical applications of such devices possible, such as non-invasive metabolic monitoring and disease diagnosis [73]. These electrochemical biosensors usually consist of three electrodes: a reference electrode, a counter electrode and a working electrode [74]. The electrochemical conversion element can sense changes in electrical characteristics caused by the generation or consumption of ions or electrons in the biometric reaction and use them as measurement parameters for health monitoring [75–77].

Furthermore, sweat can serve as an ideal and sustainable bio-energy to power future skin-interfaced electronic devices [78,79].

Temperature is a critical signal of the human body and it offers direct diagnosis of individuals with fever and hypothermia [80]. The complex metabolic changes in the human body leads to a change in temperature, which can be measured using a thermopile or thermistor [81–83] and directly integrated into flexible circuits for wearable body temperature monitoring [84,85]. Moreover, continuous measurements of body temperature can offer information to predict human diseases, for example, patients with Alzheimer's Disease display delayed temperature acrophases in their circadian rhythm [86].

Electromagnetic sensors generate spontaneous sensing signals by collecting mechanical energy [87]. Magnetic coupling between coils and permanent magnets generate voltage upon changes in magnetic field distribution generated from mechanical disturbances [88,89]. The electromagnetic core components are typically mechanically decoupled to avert direct contact and wear, enabling such sensors to withstand various humidity and temperature levels, leading to longer service life and higher durability. These electromagnetic sensors can be deployed in large numbers for multiple-location sensing in health applications such as rehabilitation and voice aid [90–92].

Utilizing body acoustic waves or surface acoustic waves, ultrasonic wearable sensors are used for detecting changes in elasticity, mass density, electrical conductivity, viscoelasticity, and other physical or chemical properties, based on the piezoelectric effect [93–95]. Moreover, compared with the previously mentioned monitoring mechanisms, which are usually limited to recording signals on the skin or superficial subcutaneous tissues, ultrasound can penetrate human tissues to a depth of several centimeters, opening a third dimension for wearable electronic devices [96].

3. Applications of wearable devices

This section summarizes the applications of wearable biosensors for the monitoring of human health, categorized by the sensing mechanism.

3.1. Optoelectronic biosensors

Fig. 2a shows an example of continuous and wireless monitoring of oxidative stress upon encapsulation of single-walled carbon nanotube fluorescent sensors within microfibers [97]. A one-step coaxial electrospinning process was used to encapsulate the nanosensors into microfiber

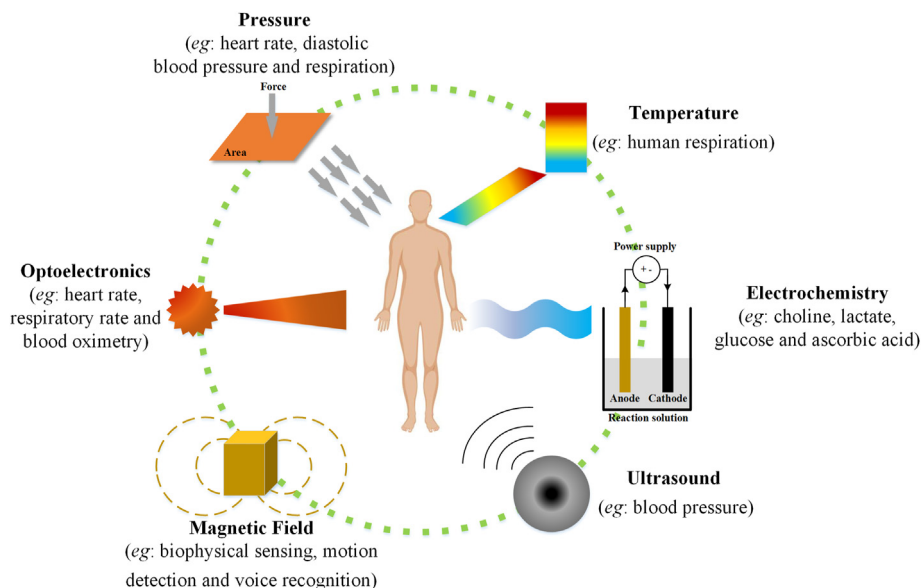


Fig. 1. Schematic diagram on the classification of common sensing mechanisms in wearable biosensors and their corresponding clinical applications.



Fig. 2. Portable and wearable electronics for optoelectronic sense: (a) Optical micro fibrous biomaterial with encapsulated nanosensor [97]; (b) Skin-interfaced biosensor for monitoring in neonatal and pediatric intensive-care units [60]; (c) Skin-interfaced biosensor for cerebral hemodynamic monitoring in pediatric care [61]; (d) Flexible and transparent wearables based on graphene sensitized with semiconducting quantum dots [98].

textiles, which was further integrated into commercial wound bandages for the monitoring of oxidative stress during wound-healing. An InGaAs camera spatially resolved the peroxide concentration on the wound surface. The ability to continuously, non-invasively monitor biochemical information via wearable technology opens the door to real-time understanding of individual physiological state, playing a potential key role in personalized medicine.

Fig. 2b and c illustrates a unique class of skin-interfaced biosensors for wireless physiological monitoring on neonatal and pediatric subjects [60, 61]. These wireless and non-invasive biosensors have the ability to measure heart rate, respiration rate, blood oxygenation, cerebral oxygenation, temperature, and advanced capabilities including non-invasive, continuous blood pressure monitoring, energy expenditure, and quantification of kangaroo mother care duration of newborns. Clinical studies conducted in neonatal and pediatric intensive-care units demonstrate the potential to improve the quality of neonatal and pediatric intensive care.

Fig. 2d shows a class of graphene-based flexible transparent wearable devices [98]. These devices were sensitized by semiconductor quantum dots and capable of monitoring of a wide range of vital signs non-invasively, including respiratory rate, heart rate, and arterial oxygen

saturation. In addition, the use of a flexible ultraviolet (UV) sensitive photodetector and the heterogeneous integration of the near field communication circuit board allowed wireless communication and power transmission between the sensor and the smartphone. This technology enables wireless detection of the UV index exposure.

3.2. Pressure biosensors

Pressure sensors have become increasingly prominent in research due to their ability in measuring mechanical disturbances continuously and quantitatively [99–103]. Although significant progress has been made in manufacturing high-performance, user-compatible pressure sensors, the trade-off between sensitivity and linear range is still a significant challenge [104–107]. Recently, Lu et al. reported an ultrathin and stretchable seism cardiography (SCG) sensing e-tattoo (Fig. 3a) [108]. The soft SCG sensor coupled with a pair of flexible gold electrodes was integrated onto an electronic tattoo platform to form a soft electric-force-acoustic cardiovascular (EMAC) sensor tattoo, which performed simultaneous electrocardiogram (ECG) and SCG measurements, as well as a blood pressure surrogate, the systolic time interval (STI), offering a simple method to continuously, non-invasively assess blood pressure.

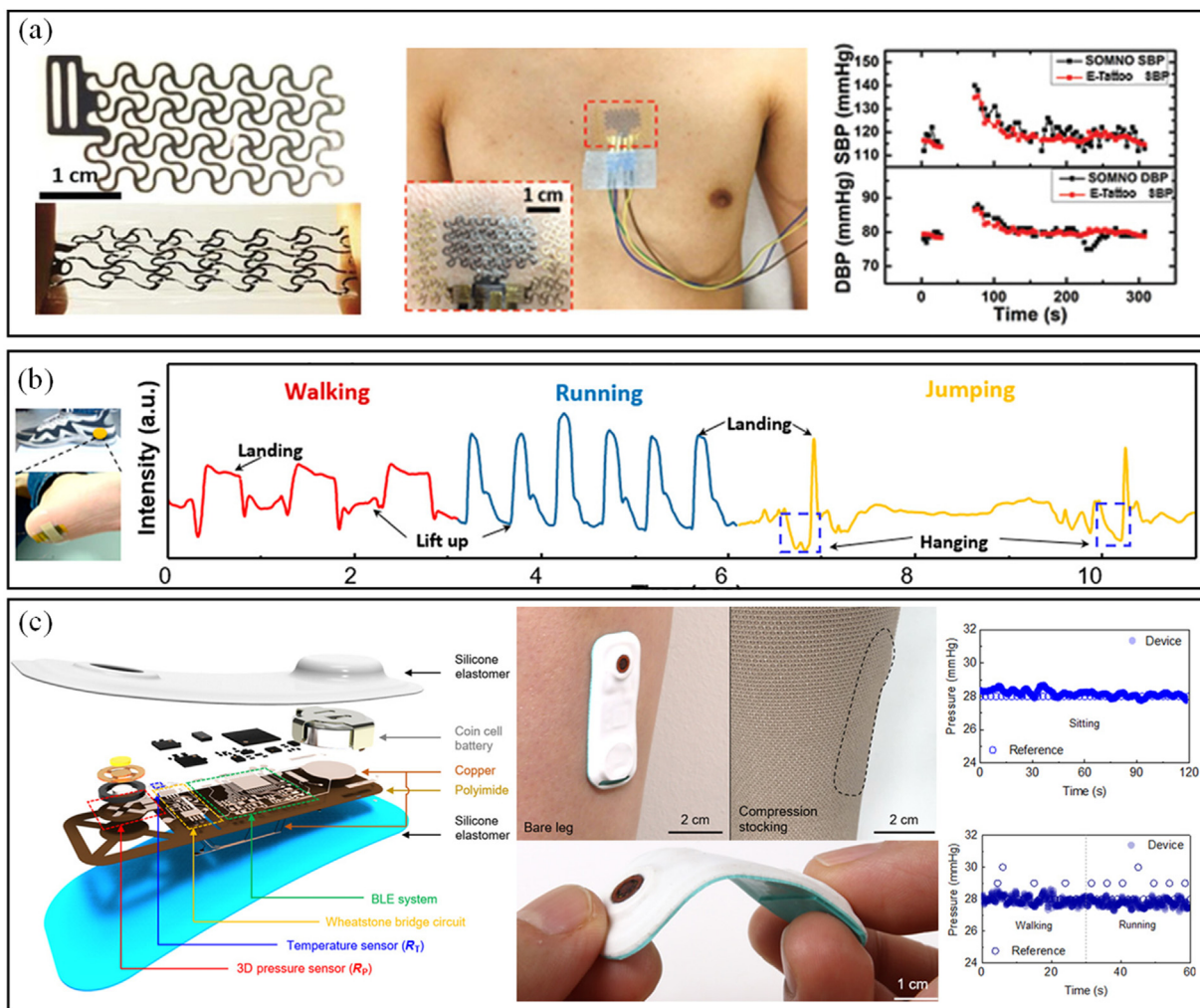


Fig. 3. Portable and wearable electronics for pressure sense: (a) Chest-laminated ultrathin and stretchable e-tattoo [108]; (b) Epidermis microstructure-inspired graphene pressure sensor with randomly distributed spinosum [109]; (c) Skin-interfaced sensor for compression therapy [110].

Fig. 3b illustrates a force-sensing structure inspired by the skin epidermis, achieved via the combination of a sandpaper template and reduced graphene oxide, forming its surface morphology with randomly distributed spinous microstructures [109]. The sensor was capable of measuring human physiological signals, such as heartbeat, phonation, and human motion, and its array was further utilized to obtain gait states of supination, neutral, and pronation. Moreover, its microstructure offered an alternative method to enhance the performance of pressure sensors and expand their potential applications in detecting human activities.

Fig. 3c introduces a wearable pressure monitoring system to quantify the pressure of therapeutic compression garments (TCGs) [110]. Studies on healthy subjects demonstrated accurate and stable monitoring performance. Clinical studies on patients of pathological symptoms showed their ability to detect the pressure exerted on a variety of skin conditions and body types. Moreover, specific demonstrations in complex actual scenarios such as sleeping, walking, and biking highlighted its continuous tracking ability, showing potential applications not only in the clinic but also in everyday life.

3.3. Electrochemical biosensors

Electrochemical biosensing technology has unique advantages including ease of miniaturization, high sensitivity, and low power consumption, rendering it suitable for wearable perspiration analysis

[111–114]. Recent work has reported and proved the feasibility of wearable electrochemical sensors for monitoring human body fluids such as sweat, saliva, and tears [115–117]. A vital requirement for the widespread use of sweat sensing equipment is to capture sufficient sweat volume without pollution, and perform in-situ quantitative analysis of multiple biomarkers related to physiological conditions such as muscle fatigue and dehydration [118–120]. Fig. 4a demonstrates a multi-channel sweat biosensor platform based on a fully integrated patch-type array for quantitative analysis of sweat [121]. A flexible and fully perspiration-powered integrated electronic skin (PPES) enabled in situ multiplexed metabolic sensing. Using multi-dimensional nanomaterial integration, this battery-free electronic skin had multi-modal sensors and lactic acid biofuel cells to obtain long-term stability (60 h of continuous operation) and high power intensity (3.5 mW cm^{-2}). The data were wirelessly transmitted to the user interface via Bluetooth.

Advances in wearable technology open doors to previously-unexplored territories, including the tracking of the biochemical correlation between physical and psychological stress, as well as other aspects of cognitive state [122–124]. Recently, Rogers et al. [125] made significant advances in designing biochemical sensors and microfluidics to support multi-mode operation for monitoring physiological signals directly related to physiological and psychological stress (Fig. 4b). These devices are capable of measuring biochemicals including cortisol, glucose, ascorbic acid (vitamin C), as well as quantifying the galvanic skin response via digital tracking, enabling noninvasive monitoring of

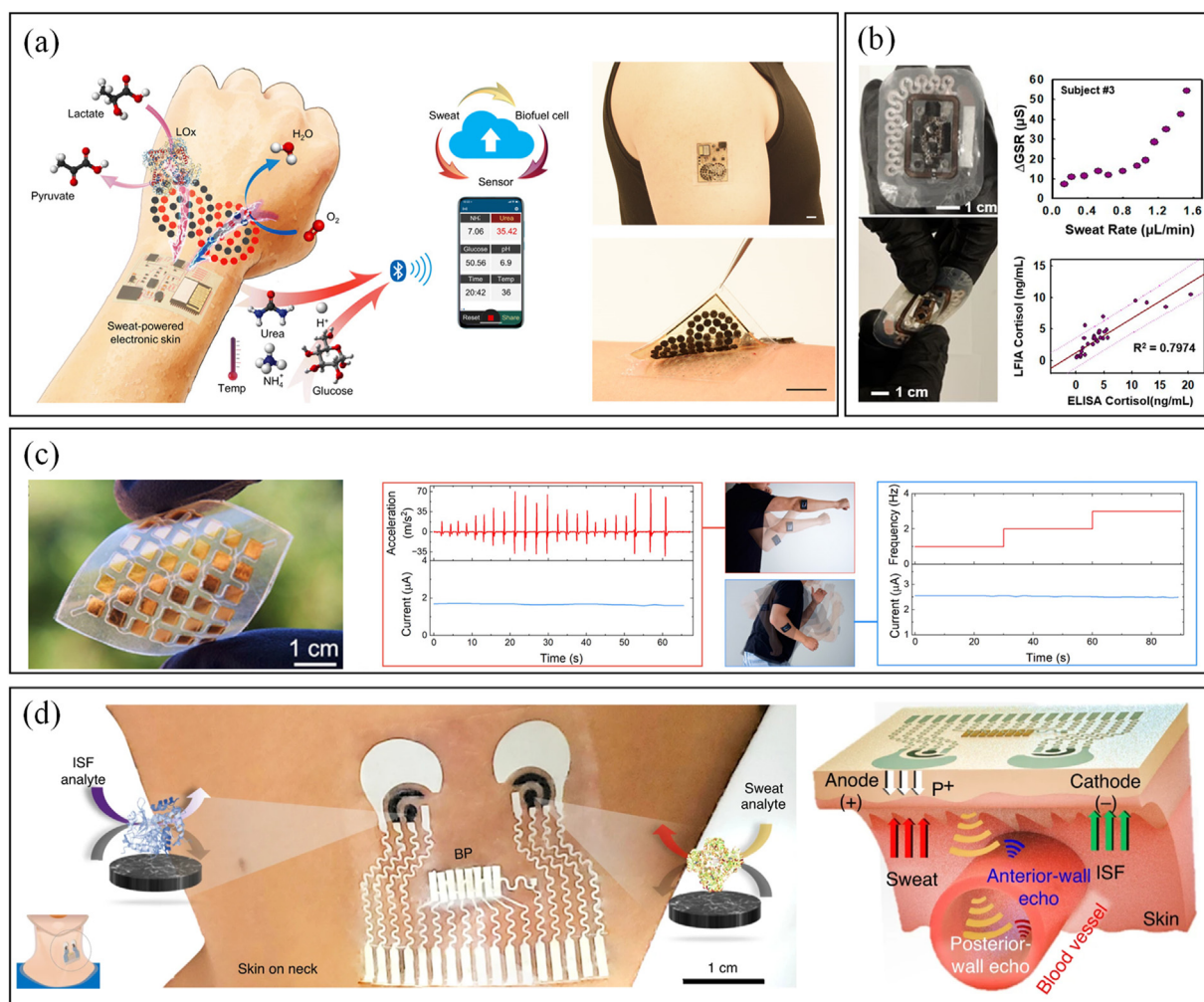


Fig. 4. Epidermal biosensors for real-time monitoring of sweat chemistry: (a) Biofuel-powered soft electronic skin with multiplexed and wireless sensing [121]; (b) Soft, skin-interfaced microfluidic system [125]; (c) Wearable freestanding electrochemical sensing system [126]; (d) Skin-worn device for the simultaneous monitoring of blood pressure and heart rate [127].

biochemical and biophysical factors related to stress.

Fig. 4c represents a scalable, disposable freestanding electrochemical sensing system (FESS), whose out-of-plane interconnects engineer a strain-isolated pathway for signal transduction [126], providing a solution to the challenge of signal fidelity during motion. Fig. 4d illustrates a stretchable, wearable sensor that monitors blood pressure, heart rate and the levels of glucose, lactate and alcohol for self-monitoring, enriching individualized understanding of physiological states during daily activities and promoting early prediction physiological complications [127]. The sensor monitors blood pressure and heart rate by ultrasonic transducers and the levels of biomarkers are measured by electrochemical sensors. The rigid and soft sensor components are integrated through considered material selection, layout design, and manufacturing engineering, forming a wearable, skin-conformal sensor with high mechanical flexibility and functional capabilities.

3.4. Other kinds of biosensors

In addition to the aforementioned sensing principles, other sensing mechanisms, such as electromagnetic, thermo-sensitive, ultrasonic, have also been utilized by wearable biosensors. Recently, a fully flexible electromechanical system sensor was developed by Huang et al. [128]. The device consisting of a multilayer flexible coil and a circular origami magnetic film was used to wrap a floating flexible magnet in it to perform wearable monitoring of mechanical displacements with good

adaptability to complex surface morphologies, as shown in Fig. 5a. Also, due to the sensor's high flexibility, it has various applications such as biophysical sensing, motion detection, voice recognition, and machine diagnosis by attaching directly to soft and curved surfaces.

Thermal sensing is a new, non-invasive skin health monitoring method. These sensors can measure the thermal characteristics of the skin at different depths, up to a few millimeters, unlike other traditional techniques based on electrical impedance [129–131]. It is worth noting that the rate and depth of human breathing reveal key physiological information for health assessment. Fig. 5b illustrates an ultrathin, skin-integrated breathing sensor utilizing the thermal convection effect [132]. The filamentous fractal design of the gold heating electrode, the micron-thin thermal sensitive sensor and the ultra-soft package ensured the flexibility and biaxial stretchability of the system. Moreover, such sensors have the ability to distinguish between different breathing patterns in real-time by detecting the breathing rate and breathing depth of the subject.

Fig. 5c represents a flexible, reusable, portable and noninvasive skin hydration sensor [133] for the monitoring of volumetric water content (up to a depth of about 1 mm). It wirelessly transmits data to smartphones via near field communication or Bluetooth [134].

Continuous detection of the central blood pressure waveforms generated from deep-tissue blood vessels has the potential to predict cardiovascular death [135–137]. Xu et al. developed a stretchable and conformal ultrasound device for non-invasive and continuous monitoring

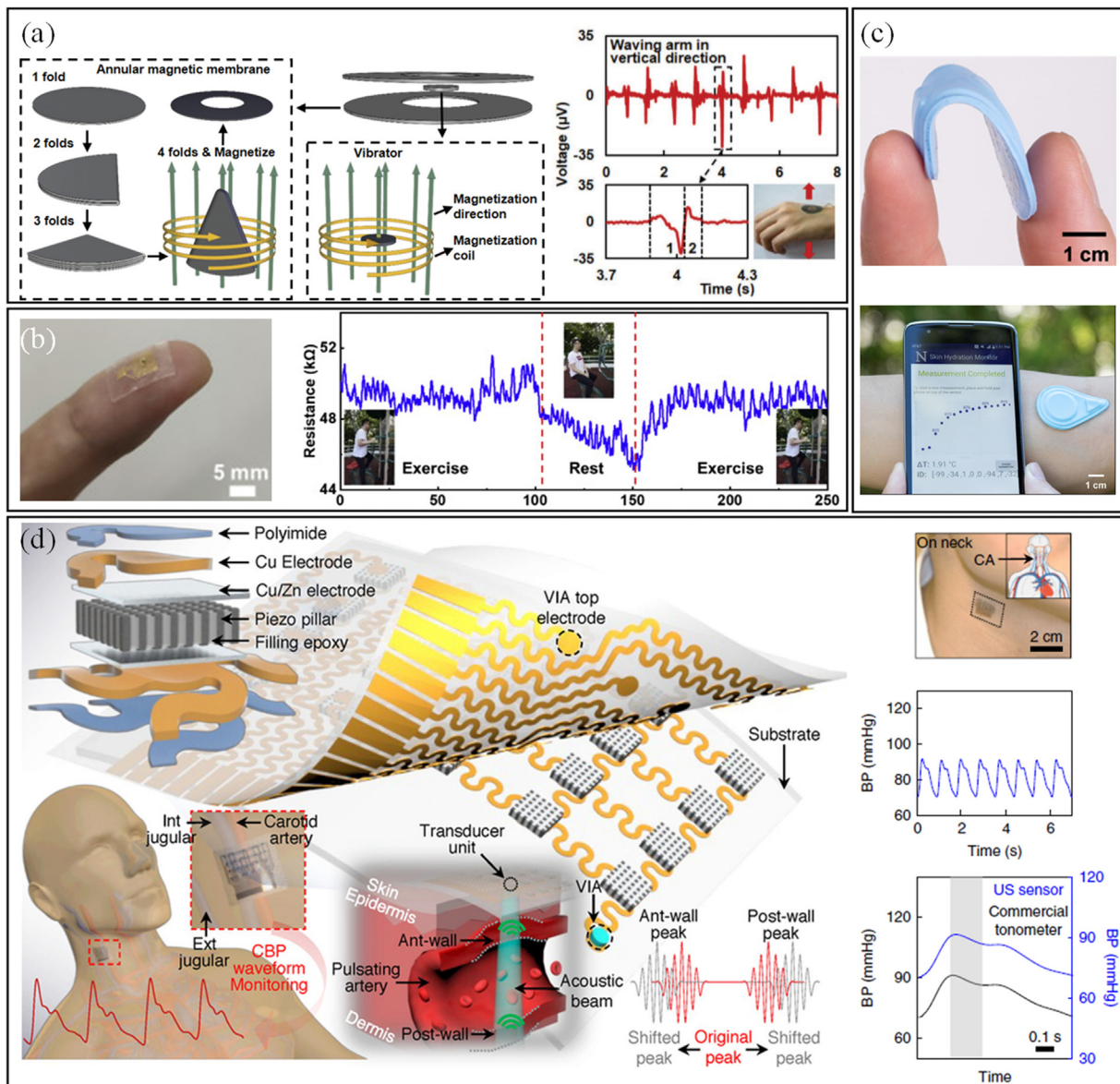


Fig. 5. Other kinds of portable and wearable biosensors for monitoring health: (a) Fully flexible electromagnetic vibration sensor [128]; (b) Ultrathin, skin-integrated respiration sensor [132]; (c) Reliable, low-cost, fully integrated hydration sensor [133]; (d) Conformal ultrasonic device for monitoring of the central blood pressure waveform [138].

of vital signs generated from deep tissues, adding a new dimension to the sensing range of conventional stretchable electronics (Fig. 5d) [138]. The wearable device was ultra-thin (240 μm) and stretchable (strain up to 60%), enabling non-invasive, continuous and accurate monitoring of cardiovascular events from multiple body locations, which could facilitate its use in various clinical environments.

4. Conclusions and outlook

Smartphone applications and commercial wrist-worn devices (such as the Apple Watch) for real-time monitoring of physical activity are becoming increasingly common in everyday life, providing large quantities of data on healthy behaviors in free-living environments [139]. Apple Watch Series 4, the first smartwatch with single-lead ECG recording based on a pressure sensor, was approved by the Food and Drug Administration (FDA) in August 2018. All ECG data recorded by the smartwatch were automatically transferred to the paired iPhone [140]. Driven by advances in big data analysis, the future of digital health heralds the integration of machine-learning-based analyses with

wearable health systems [9]. Current machine learning and big-data analytical techniques rely on high-quality data for algorithm training as well as data analysis, highlighting the importance of signal fidelity for wearable sensors [142,143]. Successful integration will provide means for patient-oriented chronic disease management, reduce the frequency of clinical visits, and provide personalized-on-demand intervention [141].

In this review, we highlighted the exciting opportunities that wearable biosensors provided for disease management. Flexible, skin-integrated biosensors provide real-time information of the body's physiological signals and health status. Moreover, digital health facilitated by wearable electronics and big data analytics holds great potential in empowering patients with real-time diagnostics tools and information. Future research on enhancing the detection accuracy of wearable sensors may expand its applications. In view of the active research on wearable biosensors and substantial commercial opportunities, flexible wearable biosensors expected to substitute current rigid sensors to make a difference in health care and personalized medicine.

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Author contribution to study

Pancheng Zhu: Writing – Original Draft, Conceptualization, Research, and Editing. Alina Y. Rwei: Supervision, Funding acquisition, Writing-Reviewing and Editing. Hanmin Peng: Editing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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