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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 circadium 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

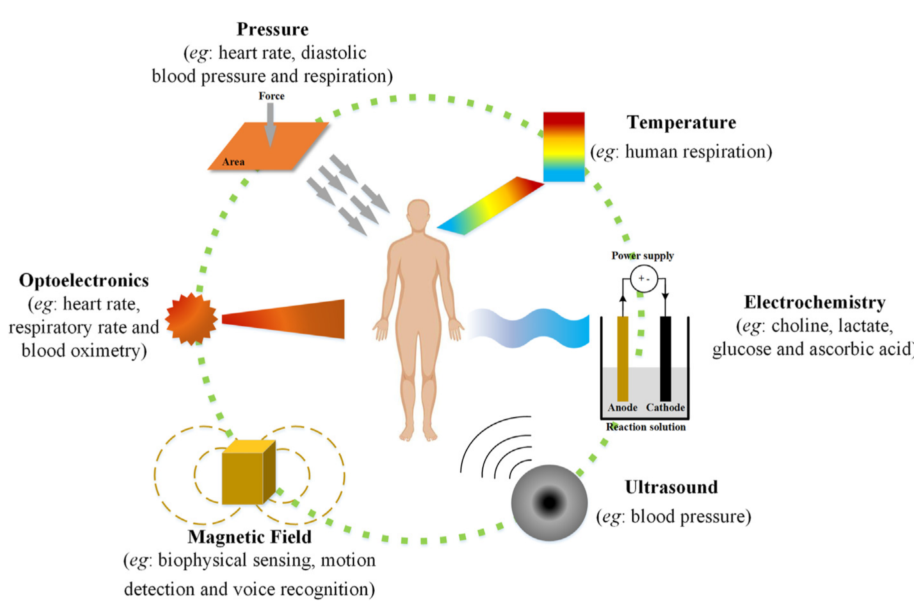

Fig. 1. Schematic diagram on the classification of common sensing mechanisms in wearable biosensors and their corresponding clinical applications.

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.

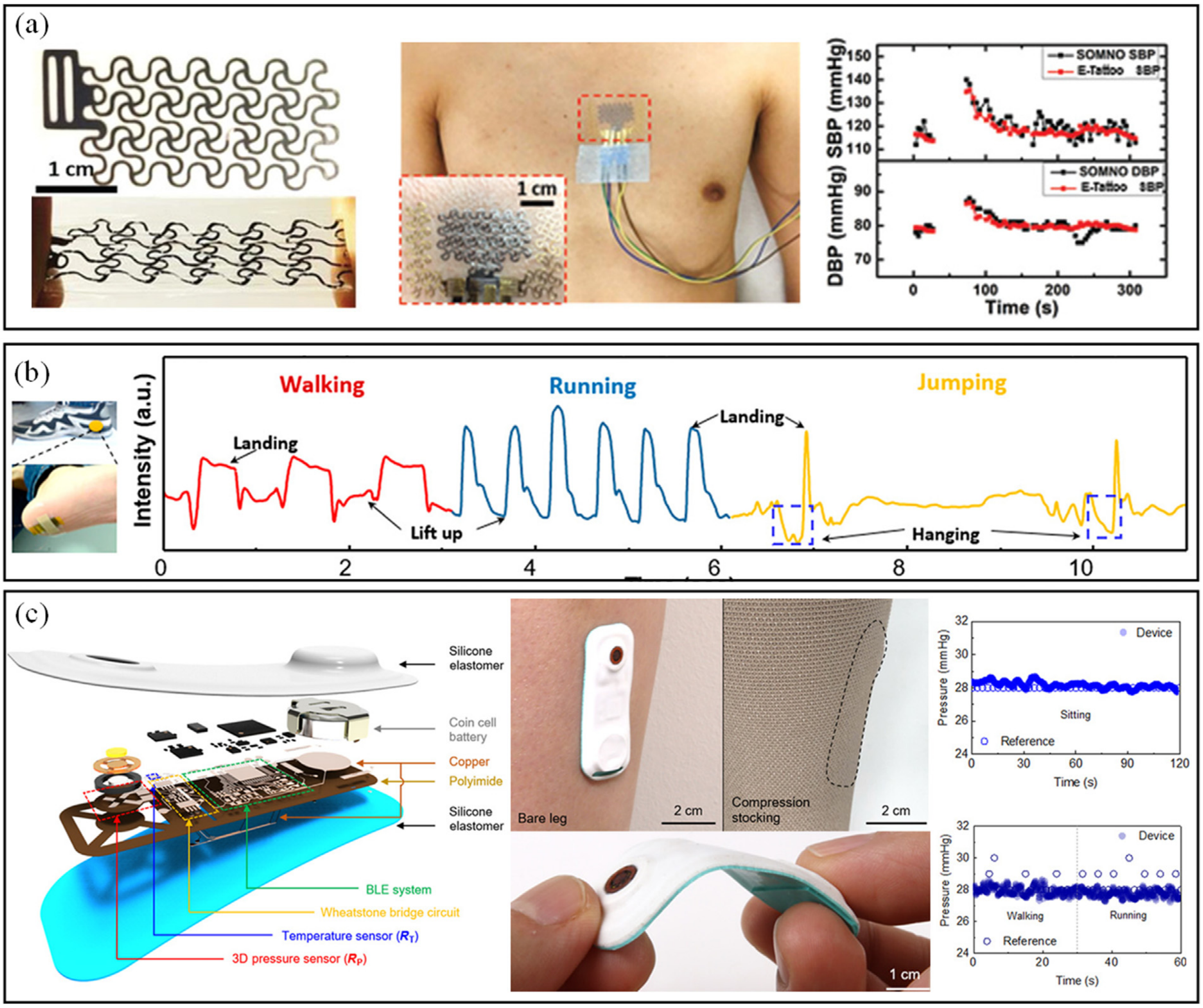

Fig. 3. Portable and wearable electronics for pressure sense: (a) Chest-laminated ultrathin and stretchable e-tattoo [108]; (b) Epidermis microstructure-inspired graphene pressure sensor with randomly distributed spinosum [109]; (c) Skin-interfaced sensor for compression therapy [110].

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-underexplored 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

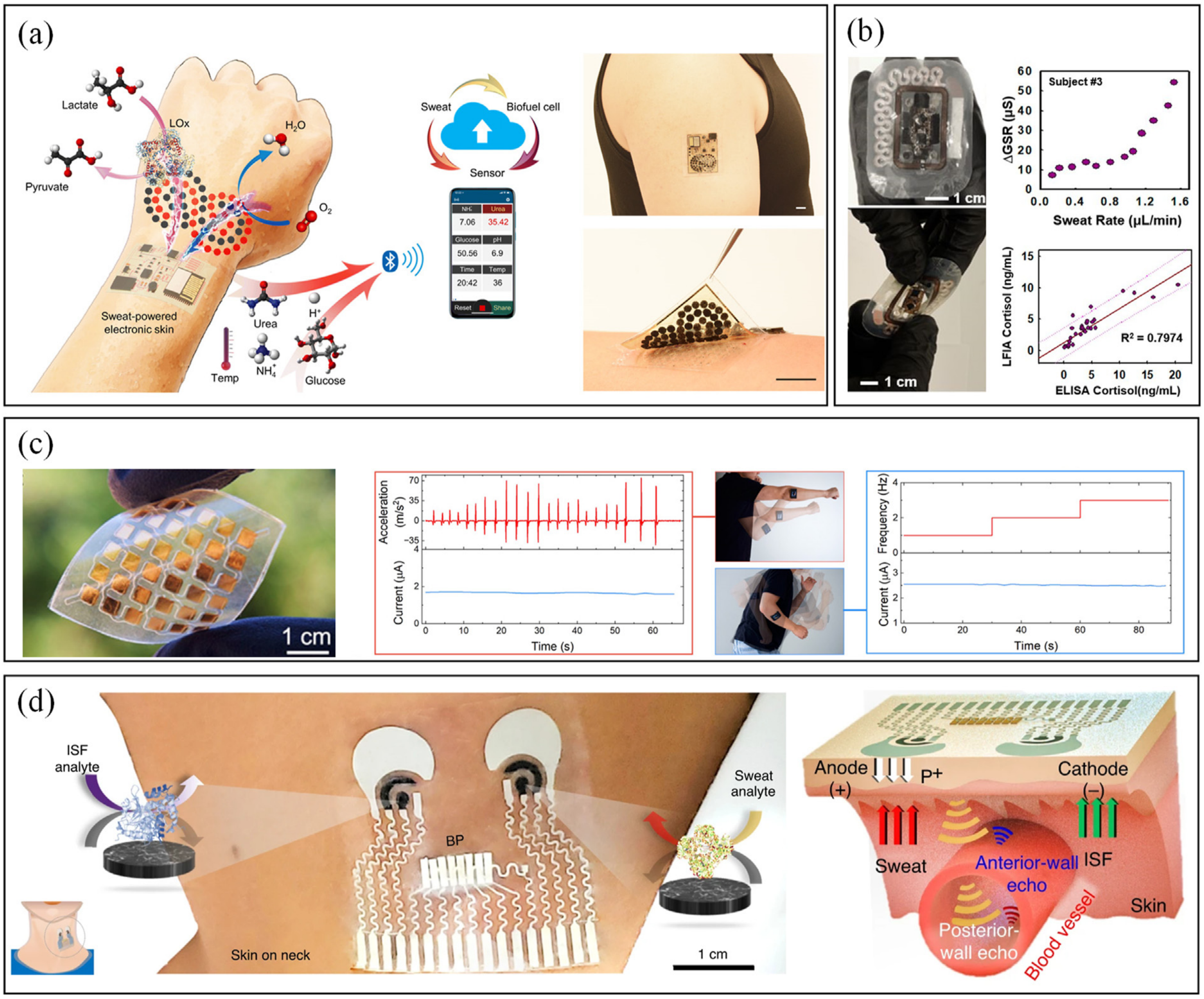

Fig. 4. Epidermal biosensors for real-time monitoring of sweat chemistry: (a) Biofuel-powered soft electronic skin with multiplexed and wireless sensing [121]; (b) Soft, skin-interfaced microfluidic system [125]; (c) Wearable freestanding electrochemical sensing system [126]; (d) Skin-worn device for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

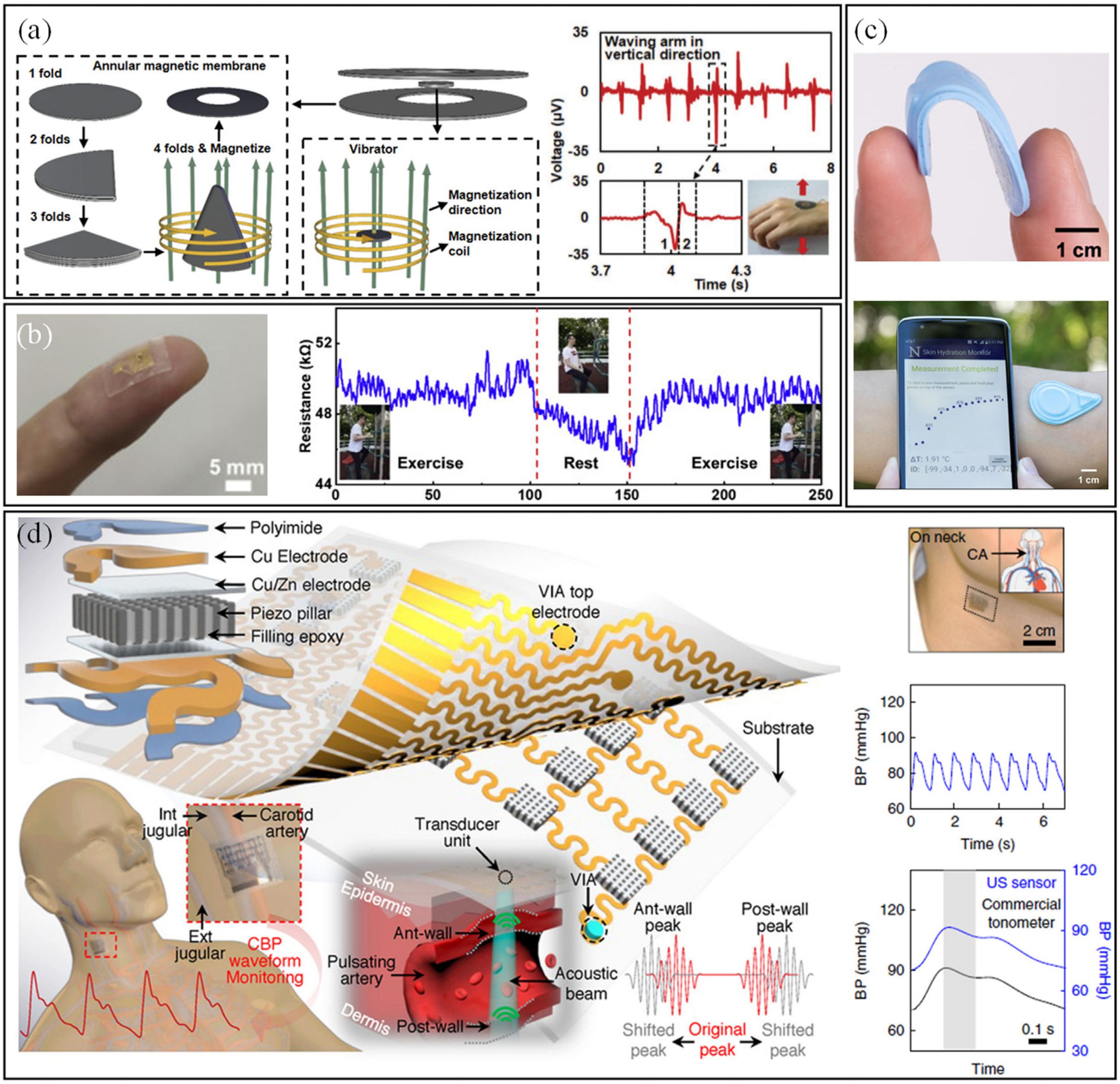

Fig. 5. Other kinds of portable and wearable biosensors for monitoring health: (a) Fully flexible electromagnetic vibration sensor [128]; (b) Ultrathin, skin-integrated respiration sensor [132]; (c) Reliable, low-cost, fully integrated hydration sensor [133]; (d) Conformal ultrasonic device for monitoring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

References

[1] Chen X, Rogers JA, Lacour SP, et al. Materials chemistry in flexible electronics. Chem Soc Rev 2019;48:1431–3.
[2] Rogers J, Bao Z, Lee TW. Wearable bioelectronics: opportunities for chemistry. Acc Chem Res 2019;52:521–2.
[3] Liu Y, Pharr M, Salvatore GA. Lab-on-skin: a review of flexible and stretchable electronics for wearable health monitoring. ACS Nano 2017;11:9614–35.
[4] Amjadi M, Kyung KU, Park I, et al. Stretchable, skin-mountable, and wearable strain sensors and their potential applications: a review. Adv Funct Mater 2016; 26:1678–98.
[5] Xu S, Jayaraman A, Rogers JA. Skin sensors are the future of health care. Nature 2019;571:319–21.
[6] Ray TR, Choi J, Bandodkar AJ, et al. Bio-integrated wearable systems: a comprehensive review. Chem Rev 2019;119:5461–533.
[7] Kim J, Campbell AS, de Ávila BEF, et al. Wearable biosensors for healthcare monitoring. Nat Biotechnol 2019;37:389–406.
[8] Quesada-González D, Merkoçi A. Mobile phone-based biosensing: an emerging "diagnostic and communication" technology. Biosens Bioelectron 2017;92: 549–62.
[9] Steinhubl SR, Muse ED, Topol EJ. The emerging field of mobile health. Sci Transl Med 2015;283:283rv3.
[10] Akhtar N, El-Safty SA, Abdelsalam ME, et al. One-pot fabrication of dendritic NiO@ carbon–nitrogen dot electrodes for screening blood glucose level in diabetes. Adv Healthc Mater 2015;4:2110–9.
[11] Al-Ogaidi I, Gou H, Al-Kazaz AKA, et al. A gold@ silica core–shell nanoparticle-based surface-enhanced Raman scattering biosensor for label-free glucose detection. Anal Chim Acta 2014;811:76–80.
[12] Chen Y, Lu B, Chen Y, et al. Breathable and stretchable temperature sensors inspired by skin. Sci Rep 2015;5:1–11.
[13] Akhtar N, Emran MY, Shenashen MA, et al. Fabrication of photo-electrochemical biosensors for ultrasensitive screening of mono-bioactive molecules: the effect of geometrical structures and crystal surfaces. J Mater Chem B 2017;5:7985–96.
[14] Miyamoto A, Lee S, Cooray NF, et al. Inflammation-free, gas-permeable, lightweight, stretchable on-skin electronics with nanomeshes. Nat Nanotechnol 2017;12:907–13.
[15] Yetisen AK, Martinez-Hurtado JL, Ünal B, et al. Wearables in medicine. Adv Mater 2018;30:1706910.
[16] Salvatore GA, Sülzle J, Dalla Valle F, et al. Biodegradable and highly deformable temperature sensors for the internet of things. Adv Funct Mater 2017;27:1702390.
[17] Roy K, Ghosh SK, Sultana A, et al. A self-powered wearable pressure sensor and pyroelectric breathing sensor based on GO interfaced PVDF nanofibers. ACS Appl Nano Mater 2019;2:2013–25.
[18] Vashist SK. Continuous glucose monitoring systems: a review. Diagnostics 2013;3: 385–412.
[19] Senior M. Novartis signs up for Google smart lens. Nat Biotechnol 2014;32:856–7.
[20] Anastasova S, Crewther B, Bembnowicz P, et al. A wearable multisensing patch for continuous sweat monitoring. Biosens Bioelectron 2017;93:139–45.
[21] Sempionatto JR, Nakagawa T, Pavinatto A, et al. Eyeglasses based wireless electrolyte and metabolite sensor platform. Lab Chip 2017;17:1834–42.
[22] Raju KSR, Taneja I, Singh SP. Utility of noninvasive biomatrices in pharmacokinetic studies. Biomed Chromatogr 2013;27:1354–66.
[23] Munje RD, Muthukumar S, Jagannath B, et al. A new paradigm in sweat based wearable diagnostics biosensors using Room Temperature Ionic Liquids (RTILs). Sci Rep 2017;7:1–12.
[24] Gao W, Emaminejad S, Nyein HYY, et al. Fully integrated wearable sensor arrays for multiplexed in situ perspiration analysis. Nature 2016;529:509–14.
[25] Huang X, Liu Y, Chen K, et al. Stretchable, wireless sensors and functional substrates for epidermal characterization of sweat. Small 2014;10:3083–90.
[26] Huang X, Yeo WH, Liu Y, et al. Epidermal differential impedance sensor for conformal skin hydration monitoring. Biointerphases 2012;7:52.
[27] Huang X, Liu Y, Cheng H, et al. Materials and designs for wireless epidermal sensors of hydration and strain. Adv Funct Mater 2014;24:3846–54.
[28] Kim J, Salvatore GA, Araki H, et al. Battery-free, stretchable optoelectronic systems for wireless optical characterization of the skin. Sci Adv 2016;2: e1600418.
[29] Park JJ, Hyun WJ, Mun SC, et al. Highly stretchable and wearable graphene strain sensors with controllable sensitivity for human motion monitoring. ACS Appl Mater Interfaces 2015;7:6317–24.
[30] Jeong JW, Kim MK, Cheng H, et al. Capacitive epidermal electronics for electrically safe, long-term electrophysiological measurements. Adv Healthc Mater 2014;3:642–8.
[31] Clark JLC, Lyons C. Electrode systems for continuous monitoring in cardiovascular surgery. Ann N Y Acad Sci 1962;102:29–45.
[32] Perumal V, Hashim U. Advances in biosensors: principle, architecture and applications. J Appl Biomed 2014;12:1–15.
[33] Palchetti I. Affinity biosensors for tumor-marker analysis. Bioanalysis 2014;6: 3417–35.
[34] Fogel R, Limson J, Seshia AA. Acoustic biosensors. Essays Biochem 2016;60(1): 101–10.
[35] Liu Y, Matharu Z, Howland MC, et al. Affinity and enzyme-based biosensors: recent advances and emerging applications in cell analysis and point-of-care testing. Anal Bioanal Chem 2012;404:1181–96.
[36] Arugula MA, Simonian A. Novel trends in affinity biosensors: current challenges and perspectives. Meas Sci Technol 2014;25:032001.
[37] Hasan A, Nurunnabi M, Morshed M, et al. Recent advances in application of biosensors in tissue engineering. BioMed Res Int 2014;2014:307519.
[38] Maiti R, Gerhardt LC, Lee ZS, et al. In vivo measurement of skin surface strain and sub-surface layer deformation induced by natural tissue stretching. J Mech Behav Biomed Mater 2016;62:556–69.
[39] Kim J, Campbell AS, Wang J. Wearable non-invasive epidermal glucose sensors: a review. Talanta 2018;177:163–70.
[40] Bandodkar AJ, Wang J. Non-invasive wearable electrochemical sensors: a review. Trends Biotechnol 2014;32:363–71.
[41] Bandodkar AJ, Jia W, Wang J. Tattoo-based wearable electrochemical devices: a review. Electroanalysis 2015;27:562–72.
[42] Piwek L, Ellis DA, Andrews S, et al. The rise of consumer health wearables: promises and barriers. PLoS Med 2016;13:e1001953.
[43] Zaleski KL, Kussman BD. Near-infrared spectroscopy in pediatric congenital heart disease. J Cardiothorac Vasc Anesth 2020;34:489–500.
[44] Yu Y, Zhang K, Zhang L, et al. Cerebral near-infrared spectroscopy (NIRS) for perioperative monitoring of brain oxygenation in children and adults. Cochrane Database Syst Rev 2018;1:CD010947.
[45] Chakravarti S, Srivastava S, Mittnacht AJC. Near infrared spectroscopy (NIRS) in children. Seminars in cardiothoracic and vascular anesthesia. Sage CAvol. 12. Los Angeles, CA: SAGE Publications; 2008. p. 70–9.
[46] Dagdeviren C, Su Y, Joe P, et al. Conformable amplified lead zirconate titanate sensors with enhanced piezoelectric response for cutaneous pressure monitoring. Nat Commun 2014;5:1–10.
[47] Yao HB, Ge J, Wang CF, et al. A flexible and highly pressure-sensitive graphene–polyurethane sponge based on fractured microstructure design. Adv Mater 2013;25:6692–8.
[48] Chou HH, Nguyen A, Chortos A, et al. A chameleon-inspired stretchable electronic skin with interactive colour changing controlled by tactile sensing. Nat Commun 2015;6:1–10.
[49] Qiang L, Vaddiraju S, Rusling JF, et al. Highly sensitive and reusable Pt-black microfluidic electrodes for long-term electrochemical sensing. Biosens Bioelectron 2010;26:682–8.
[50] Wang Z, Wang X, Li M, et al. Highly sensitive flexible magnetic sensor based on anisotropic magnetoresistance effect. Adv Mater 2016;28:9370–7.
[51] Moser Y, Gijs MAM. Miniaturized flexible temperature sensor. J Microelectromech Syst 2007;16:1349–54.
[52] Rodrigues D, Barbosa AI, Rebelo R, et al. Skin-integrated wearable systems and implantable biosensors: a comprehensive review. Biosensors 2020;10:79.
[53] Pang C, Koo JH, Nguyen A, et al. Highly skin-conformal microhairy sensor for pulse signal amplification. Adv Mater 2015;27:634–40.
[54] Asrami PN, Tehrani MS, Azar PA, et al. Impedimetric glucose biosensor based on nanostructure nickel oxide transducer fabricated by reactive RF magnetron sputtering system. J Electroanal Chem 2017;801:258–66.
[55] Chung HU, Kim BH, Lee JY, et al. Binodal, wireless epidermal electronic systems with in-sensor analytics for neonatal intensive care. Science 2019;363:eaau0780.
[56] Kwon K, Heo SY, Yoo I, et al. Miniaturized, light-adaptive, wireless dosimeters autonomously monitor exposure to electromagnetic radiation. Sci Adv 2019;5: eaay2462.
[57] Zhang H, Gutruf P, Meacham K, et al. Wireless, battery-free optoelectronic systems as subdermal implants for local tissue oximetry. Sci Adv 2019;5:eaaw0873.
[58] Mendelson Y, Ochs BD. Noninvasive pulse oximetry utilizing skin reflectance photoplethysmography. IEEE (Inst Electr Electron Eng) Trans Biomed Eng 1988; 35:798–805.
[59] Heo SY, Kim J, Gutruf P, et al. Wireless, battery-free, flexible, miniaturized dosimeters monitor exposure to solar radiation and to light for phototherapy. Sci Transl Med 2018;10:aah3924.
[60] Chung HU, Rwei AY, Hourlier-Fargette A, et al. Skin-interfaced biosensors for advanced wireless physiological monitoring in neonatal and pediatric intensive-care units. Nat Med 2020;26:418–29.
[61] Rwei AY, Lu W, Wu C, et al. A wireless, skin-interfaced biosensor for cerebral hemodynamic monitoring in pediatric care. In: Proceedings of the national academy of sciences, vol. 117; 2020. p. 31674–84.

[62] Sharma T, Aroom K, Naik S, et al. Flexible thin-film PVDF-TrFE based pressure sensor for smart catheter applications. Ann Biomed Eng 2013;41:744–51.
[63] Liu Z, Ma Y, Ouyang H, et al. Transcatheter self-powered ultrasensitive endocardial pressure sensor. Adv Funct Mater 2019;29:1807560.
[64] Schwartz G, Tee BCK, Mei J, et al. Flexible polymer transistors with high pressure sensitivity for application in electronic skin and health monitoring. Nat Commun 2013;4:1–8.
[65] Shin J, Liu Z, Bai W, et al. Bioresorbable optical sensor systems for monitoring of intracranial pressure and temperature. Sci Adv 2019;5:eaaw1899.
[66] Dagdeviren C, Su Y, Joe P, et al. Conformable amplified lead zirconate titanate sensors with enhanced piezoelectric response for cutaneous pressure monitoring. Nat Commun 2014;5:1–10.
[67] Zhu P, Peng H, Lu X, et al. A steerable miniature legged robot based on piezoelectric bending actuators. Smart Mater Struct 2020;29:45009.
[68] Wang L, Hofmann V, Bai F, et al. A novel additive manufactured three-dimensional piezoelectric transducer: systematic modeling and experimental validation. Mech Syst Signal Process 2019;114:346–65.
[69] Li X, Yao Z. Analytical modeling and experimental validation of a V-shape piezoelectric ultrasonic transducer. Smart Mater Struct 2016;25:75026.
[70] Yang L, Qiu T, Shen M, et al. Metal-organic frameworks Co3 [Co (CN) 6]. 2: a promising candidate for dramatically reinforcing the piezoelectric activity of PVDF. Compos Sci Technol 2020;196:108232.
[71] Zhu SE, Krishna Ghatkesar M, Zhang C, et al. Graphene based piezoresistive pressure sensor. Appl Phys Lett 2013;102(16):161904. Composites Part A: Applied Science and Manufacturing 2020; 132: 105820.
[72] Sonner Z, Wilder E, Heikenfeld J, et al. The microfluidics of the eccrine sweat gland, including biomarker partitioning, transport, and biosensing implications. Biomicrofluidics 2015;9:31301.
[73] Emaminejad S, Gao W, Wu E, et al. Autonomous sweat extraction and analysis applied to cystic fibrosis and glucose monitoring using a fully integrated wearable platform. Proc Natl Acad Sci Unit States Am 2017;114:4625–30.
[74] Hauke A, Simmers P, Ojha YR, et al. Complete validation of a continuous and blood-correlated sweat biosensing device with integrated sweat stimulation. Lab Chip 2018;18:3750–9.
[75] Bandodkar AJ, López CS, Mohan AMV, et al. All-printed magnetically self-healing electrochemical devices. Sci Adv 2016;2:e1601465.
[76] Lee H, Song C, Hong YS, et al. Wearable/disposable sweat-based glucose monitoring device with multistage transdermal drug delivery module. Sci Adv 2017;3:e1601314.
[77] Hong YJ, Lee H, Kim J, et al. Multifunctional wearable system that integrates sweat-based sensing and vital-sign monitoring to estimate pre-/post-exercise glucose levels. Adv Funct Mater 2018;28:1805754.
[78] Nyein HYY, Tai LC, Ngo QP, et al. A wearable microfluidic sensing patch for dynamic sweat secretion analysis. ACS Sens 2018;3:944–52.
[79] Bandodkar AJ, Gutruf P, Choi J, et al. Battery-free, skin-interfaced microfluidic/ electronic systems for simultaneous electrochemical, colorimetric, and volumetric analysis of sweat. Sci Adv 2019;5:eaav3294.
[80] Dagdeviren C, Joe P, Tuzman OL, et al. Recent progress in flexible and stretchable piezoelectric devices for mechanical energy harvesting, sensing and actuation. Extreme Mech Lett 2016;9:269–81.
[81] Liu Y, Xu Y, Avila R, et al. 3D printed microstructures for flexible electronic devices. Nanotechnology 2019;30:414001.
[82] Hong YJ, Jeong H, Cho KW, et al. Wearable and implantable devices for cardiovascular healthcare: from monitoring to therapy based on flexible and stretchable electronics. Adv Funct Mater 2019;29:1808247.
[83] Pang Y, Jian J, Tu T, et al. Wearable humidity sensor based on porous graphene network for respiration monitoring. Biosens Bioelectron 2018;116:123–9.
[84] Huang S, Liu Y, Zhao Y, et al. Flexible electronics: stretchable electrodes and their future. Adv Funct Mater 2019;29:1805924.
[85] Yang JC, Mun J, Kwon SY, et al. Electronic skin: recent progress and future prospects for skin-attachable devices for health monitoring, robotics, and prosthetics. Adv Mater 2019;31:1904765.
[86] Satlin A, Volicer L, Stopa EG, et al. Circadian locomotor activity and core-body temperature rhythms in Alzheimer's disease. Neurobiol Aging 1995;16:765–71.
[87] Yang B, Lee C, Xiang W, et al. Electromagnetic energy harvesting from vibrations of multiple frequencies. J Micromech Microeng 2009;19:035001.
[88] Beeby SP, Torah RN, Tudor MJ, et al. A micro electromagnetic generator for vibration energy harvesting. J Micromech Microeng 2007;17:1257.
[89] Donelan JM, Li Q, Naing V, et al. Biomechanical energy harvesting: generating electricity during walking with minimal user effort. Science 2008;319:807–10.
[90] Zi Y, Lin L, Wang J, et al. Triboelectric–pyroelectric–piezoelectric hybrid cell for high-efficiency energy-harvesting and self-powered sensing. Adv Mater 2015;27: 2340–7.
[91] Vivekananthan V, Chandrasekhar A, Alluri NR, et al. Fe2O3 magnetic particles derived triboelectric-electromagnetic hybrid generator for zero-power consuming seismic detection. Nano Energy 2019;64:103926.
[92] Zhang K, Wang X, Yang Y, et al. Hybridized electromagnetic–triboelectric nanogenerator for scavenging biomechanical energy for sustainably powering wearable electronics. ACS Nano 2015;9:3521–9.
[93] Wain RA, Lyon RT, Veith FJ, et al. Accuracy of duplex ultrasound in evaluating carotid artery anatomy before endarterectomy. J Vasc Surg 1998;27:235–44.
[94] Peng H, Qian X, Mao L, et al. Ultrafast ultrasound imaging in acoustic microbubble trapping. Appl Phys Lett 2019;115:203701.
[95] Howard G, Sharrett AR, Heiss G, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. Stroke 1993;24:1297–304.
[96] Zhu P, Peng H. Theory and method of temperature control for drug release in hydrogel phantom of gastric mucosa in vitro. J Appl Phys 2021;129:214506.
[97] Safaee MM, Gravely M, Roxbury D. A wearable optical microfibrous biomaterial with encapsulated nanosensors enables wireless monitoring of oxidative stress. Adv Funct Mater 2021;31:2006254.
[98] Polat EO, Mercier G, Nikitskiy I, et al. Flexible graphene photodetectors for wearable fitness monitoring. Sci Adv 2019;5:eaaw7846.
[99] Pang C, Lee GY, Kim T, et al. A flexible and highly sensitive strain-gauge sensor using reversible interlocking of nanofibres. Nat Mater 2012;11:795–801.
[100] Wu W, Wen X, Wang ZL. Taxel-addressable matrix of vertical-nanowire piezotronic transistors for active and adaptive tactile imaging. Science 2013;340: 952–7.
[101] Pan L, Chortos A, Yu G, et al. An ultra-sensitive resistive pressure sensor based on hollow-sphere microstructure induced elasticity in conducting polymer film. Nat Commun 2014;5:1–8.
[102] Wang X, Que M, Chen M, et al. Full dynamic-range pressure sensor matrix based on optical and electrical dual-mode sensing. Adv Mater 2017;29:1605817.
[103] Yeom C, Chen K, Kiriya D, et al. Large-area compliant tactile sensors using printed carbon nanotube active-matrix backplanes. Adv Mater 2015;27:1561–6.
[104] Choong CL, Shim MB, Lee BS, et al. Highly stretchable resistive pressure sensors using a conductive elastomeric composite on a micropyramid array. Adv Mater 2014;26:3451–8.
[105] Zhao J, Wang G, Yang R, et al. Tunable piezoresistivity of nanographene films for strain sensing. ACS Nano 2015;9:1622–9.
[106] Wang C, Li X, Gao E, et al. Carbonized silk fabric for ultrastretchable, highly sensitive, and wearable strain sensors. Adv Mater 2016;28:6640–8.
[107] Ryu S, Lee P, Chou JB, et al. Extremely elastic wearable carbon nanotube fiber strain sensor for monitoring of human motion. ACS Nano 2015;9:5929–36.
[108] Ha T, Tran J, Liu S, et al. A chest-laminated ultrathin and stretchable E-tattoo for the measurement of electrocardiogram, seismocardiogram, and cardiac time intervals. Adv Sci 2019;6(14):1900290.
[109] Pang Y, Zhang K, Yang Z, et al. Epidermis microstructure inspired graphene pressure sensor with random distributed spinosum for high sensitivity and large linearity. ACS Nano 2018;12:2346–54.
[110] Park Y, Kwon K, Kwak SS, et al. Wireless, skin-interfaced sensors for compression therapy. Sci Adv 2020;6:eabe1655.
[111] Park Y, Franz K, Ryu H, et al. Three-dimensional, multifunctional neural interfaces for cortical spheroids and engineered assembloids. Sci Adv 2021;7:eabf9153.
[112] Bandodkar AJ, Jeerapan I, Wang J. Wearable chemical sensors: present challenges and future prospects. ACS Sens 2016;1:464–82.
[113] Matzeu G, Florea L, Diamond D. Advances in wearable chemical sensor design for monitoring biological fluids. Sensor Actuator B Chem 2015;211:403–18.
[114] Windmiller JR, Wang J. Wearable electrochemical sensors and biosensors: a review[J]. Electroanalysis 2013;25:29–46.
[115] Mannoor MS, Tao H, Clayton JD, et al. Graphene-based wireless bacteria detection on tooth enamel. Nat Commun 2012;3:1–9.
[116] Koh A, Kang D, Xue Y, et al. A soft, wearable microfluidic device for the capture, storage, and colorimetric sensing of sweat. Sci Transl Med 2016;8. 366ra165-366ra165.
[117] Kim J, Imani S, de Araujo WR, et al. Wearable salivary uric acid mouthguard biosensor with integrated wireless electronics. Biosens Bioelectron 2015;74: 1061–8.
[118] Lee H, Choi TK, Lee YB, et al. A graphene-based electrochemical device with thermoresponsive microneedles for diabetes monitoring and therapy. Nat Nanotechnol 2016;11:566–72.
[119] Jeerapan I, Sempionatto JR, Pavinatto A, et al. Stretchable biofuel cells as wearable textile-based self-powered sensors. J Mater Chem 2016;4:18342–53.
[120] Imani S, Bandodkar AJ, Mohan AMV, et al. A wearable chemical–electrophysiological hybrid biosensing system for real-time health and fitness monitoring. Nat Commun 2016;7:1–7.
[121] Yu Y, Nassar J, Xu C, et al. Biofuel-powered soft electronic skin with multiplexed and wireless sensing for human-machine interfaces. Sci Robot 2020;5:eaaz7946.
[122] Heikenfeld J, Jajack A, Rogers J, et al. Wearable sensors: modalities, challenges, and prospects. Lab Chip 2018;18:217–48.
[123] Stoppa M, Chiolerio A. Wearable electronics and smart textiles: a critical review. Sensors 2014;14:11957–92.
[124] Jin H, Abu-Raya YS, Haick H. Advanced materials for health monitoring with skin-based wearable devices. Adv Healthc Mater 2017;6(11):1700024.
[125] Kim S, Lee B, Reeder JT, et al. Soft, skin-interfaced microfluidic systems with integrated immunoassays, fluorometric sensors, and impedance measurement capabilities. Proc Natl Acad Sci Unit States Am 2020;117:27906–15.
[126] Zhao Y, Wang B, Hojaiji H, et al. A wearable freestanding electrochemical sensing system. Sci Adv 2020;6:eaaz0007.
[127] Sempionatto JR, Lin M, Yin L, et al. An epidermal patch for the simultaneous monitoring of haemodynamic and metabolic biomarkers. Nat Biomed Eng 2021;5: 737–48.
[128] Zhao Y, Gao S, Zhang X, et al. Fully flexible electromagnetic vibration sensors with annular field confinement origami magnetic membranes. Adv Funct Mater 2020; 30:2001553.
[129] Madhvapathy SR, Ma Y, Patel M, et al. Epidermal electronic systems for measuring the thermal properties of human skin at depths of up to several millimeters. Adv Funct Mater 2018;28:1802083.
[130] Krishnan SR, Su CJ, Xie Z, et al. Wireless, battery-free epidermal electronics for continuous, quantitative, multimodal thermal characterization of skin. Small 2018;14:1803192.

[131] Webb RC, Bonifas AP, Behnaz A, et al. Ultrathin conformal devices for precise and continuous thermal characterization of human skin. Nat Mater 2013;12:938–44.
[132] Liu Y, Zhao L, Avila R, et al. Epidermal electronics for respiration monitoring via thermo-sensitive measuring. Mater Today Phys 2020;13:100199.
[133] Madhvapathy SR, Wang H, Kong J, et al. Reliable, low-cost, fully integrated hydration sensors for monitoring and diagnosis of inflammatory skin diseases in any environment. Sci Adv 2020;6:eabd7146.
[134] Kwon K, Wang H, Lim J, et al. Wireless, soft electronics for rapid, multisensor measurements of hydration levels in healthy and diseased skin. In: Proceedings of the national academy of sciences of the United States of America, vol. 118; 2021, e2020398118.
[135] Trudeau L. Central blood pressure as an index of antihypertensive control: determinants and potential value. Can J Cardiol 2014;30:S23–8.
[136] McEniery CM, Cockcroft JR, Roman MJ, et al. Central blood pressure: current evidence and clinical importance. Eur Heart J 2014;35:1719–25.
[137] Ding FH, Fan WX, Zhang RY, et al. Validation of the noninvasive assessment of central blood pressure by the SphygmoCor and Omron devices against the invasive catheter measurement. Am J Hypertens 2011;24:1306–11.
[138] Wang C, Li X, Hu H, et al. Monitoring of the central blood pressure waveform via a conformal ultrasonic device. Nat Biomed Eng 2018;2:687–95.
[139] Hicks JL, Althoff T, Kuhar P, et al. Best practices for analyzing large-scale health data from wearables and smartphone apps. NPJ Dig Med 2019;2:1–12.
[140] Behzadi A, Sepehri Shamloo A, Mouratis K, et al. Feasibility and reliability of smartwatch to obtain 3-lead electrocardiogram recordings. Sensors 2020;20:5074.
[141] Kumar S, Nilsen WJ, Abernethy A, et al. Mobile health technology evaluation: the mHealth evidence workshop. Am J Prev Med 2013;45:228–36.
[142] Shuai X, Ayra H, Bv I, et al. Wireless skin sensors for physiological monitoring of infants in low-income and middle-income countries-ScienceDirect. Lancet Dig Health 2021;3:266–73.
[143] Chen RJ, Lu MY, Chen TY, et al. Synthetic data in machine learning for medicine and healthcare. Nat Biomed Eng 2021;5:493–7.