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Flexible Miniaturized Sensor Technologies for Long-Term Physiological Monitoring

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Physiological monitoring can provide detailed information about health conditions, and therefore presents great potentials for personalized healthcare. Flexible miniaturized sensors (FMS) for physiological monitoring have garnered significant attention because of their wide applications in collecting health-related information, evaluating and managing the state of human wellness in long term. In this review, we focus on the time scale of human physiological monitoring, the needs and advances in miniaturized technologies for long-term monitoring in typical applications. We also discuss the rational sample sources of FMS to select proper strategies for specific monitoring cases. Further, existing challenges and promising prospects are also presented.

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INTRODUCTION

Health monitoring that measures and evaluates physiological signals generated by the human body can provide detailed information about human wellness, thus presenting great potentials for personalized healthcare[1]. Monitoring the level changes of various biomarkers of diseases and health factors (i.e., invigorating and debilitating factors that affect health) can unveil key insight for relevant disease exacerbation or health improvement[2–5]. So it is highly appreciated to assess health-related indices for evaluating trends of health status in the required time scale (Fig. 1). In addition, the specific time required for different monitoring tasks varies (i.e., minutes to decades with a specific frequency) for different physiological markers in different body situations and user groups. Therefore, it is important to investigate the demanded time scale of certain physiological monitoring cases. Here, we define the duration of monitoring that can meet the need of an application as long-term monitoring. For different cases, the duration required for long-term monitoring varies. Figure 2 summarizes the required time scales for some diseases and health-related factors (Practical demands), and the duration that can be monitored by the currently commercial products and research prototypes (Existing methods). Long-term monitoring is especially crucial in disease situations where the instantaneous change of related signals can indicate serious pathological consequences. For example, the abnormal blood glucose level in diabetics and high blood pressure in cardiovascular patients can threaten life. For the healthy community, long-term monitoring is helpful to evaluate the state of fitness, prevent disease and prolong health condition. Therefore, long-term monitoring is of significant importance to disease and health management and devices capable of meeting such temporal demand are highly appreciated.

But, unfortunately, the existing technology for monitoring turns out to fail to match the required time scale in many applications perfectly. For example, till now, many clinical products serve as useful platforms, *e.g.*, CT (computed tomography), MRI (magnetic resonance imaging) and HPLC (high performance liquid chromatography), to monitor physiological signals and diagnose diseases. However, these bulky instruments are not suitable for long-term monitoring because of their high cost and limited accessibility (i.e., only available in hospital). The device for long-term monitoring is expected to work in a user-friendly manner with features of miniaturized size, good biocompatibility and causing minor impact on daily activities. For this sake, sensors with miniaturized size and perform in a portable or wearable format are highly appreciated for such uses.

Besides, a variety of requirements in designing devices for long-term monitoring, especially in terms of operation time and detection frequency, have also been proposed to better popularize this advanced technology to the public. (1) The monitoring results should be reliable and rapid. This is an essential point for the health monitoring technology, especially for sensors aiming at disease monitoring. Because inaccurate monitoring results may lead to an incorrect judgment of the disease tendency and thus fail to reflect the patient's real situation. Long detecting time hinders the acquirement of timely information of metabolites, and may cause severe consequences like misdiagnosis because metabolites in body fluid always vary along with time. Therefore, reliable and rapid detection is necessary to accurately and timely analyze biomarkers. (2) Sensors should be easy to use everywhere with a high frequency, so it is highly desirable to be flexible, equipment-free, low-cost and tolerant to complex and changing environments (*e.g.*, low/high temperature, low/high humidity, ionic contamination from sweat, ultra-large stretch, *etc.*) during monitoring for a long term. Such all-environment compatibility is believed to broaden the application prospect of long-term sensing devices for diverse monitoring tasks in various conditions. To sum up, the ideal sensors for physiological monitoring are anticipated to be **u**ser-friendly, **m**iniaturized, **b**iocompatible, **r**eliable and rapid, **e**quipment-free, **l**ong-term, **l**ow-cost, and **a**ll-environment-compatible (**UMBRELLA**).

Recently, there are some reviews about continuous health monitoring using flexible and wearable sensors. However, considerations in time-scale of monitoring tasks and related flexible miniaturized sensors (FMS) technologies are unexpectedly absent. In this review, we focus on the time scale of human health

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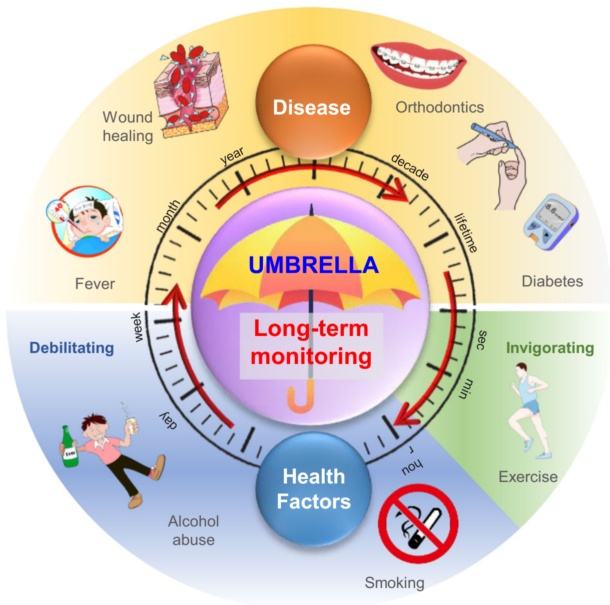

Fig. 1 Schematic illustration of the main applications of human physiological monitoring with different time scales. The time scale for monitoring of diseases and invigorating and debilitating health factors spans from minutes to decades.

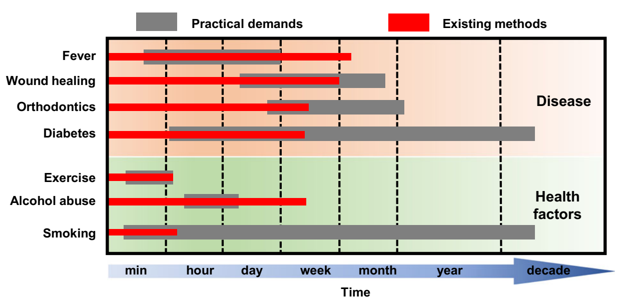

Fig. 2 The time scale of human physiological monitoring. The monitoring duration demanded by practical applications and realized by existing methods for typical diseases and health factors are analyzed.

monitoring, including monitoring duration and detection frequency, of both practical needs and existing achievement. Besides, rational sample sources of FMS are discussed. The review finally concludes an overview of key challenges and a summary of ongoing opportunities where advances in long-term physiological monitoring show promises to propel scientific researches and products transformation for personalized healthcare.

FMS TECHNOLOGIES

FMS usually have small sizes (from nano level to several centimeters) and lightweight (from a few to hundreds of grams). The popular form factors of FMS in a portable or wearable format are suitable for users to carry around and cause negligible impact to daily activities, making them highly appreciated and ideal for long-term monitoring. Further, these devices can be available at home without the need of bulky equipment and work in a user-friendly manner, so the user compliance for long-term monitoring can be improved. In addition, FMS are usually low-cost, alleviating the financial burden and cultivating users' willingness of health monitoring for a long time. FMS can be divided into three categories, i.e., portable devices, wearable devices and implanted sensors (Table 1).

Table 1. Miniaturized sensor technologies.

Miniaturized sensor technologies		UMBRELLA standard								
		User-friendly	Miniaturized (size)	Biocompatible (risk)	Reliable	Rapid (detection time)	Equipment-free	Long-term (working period)	Low-cost	All-environment-compatible
Portable devices	Paper-based test strips	Y	cm level	Infection (blood); No risk (other biofluids)	Y	Minutes	Y	Disposable	Y	N
	Microfluidic chips	Y	cm level		Y	Minutes	Y	Disposable	Y	N
Wearable devices	Accessories-like smart devices	Y	mm level to cm level	Y	Y	Seconds	Y	Days to months	Y	Y
	Flexible devices	Y	cm level	Y	Y	Seconds	Y	Days	Y	Y
	E-skin	Y	Coin-sized patch	Y	Y	Seconds	Y	Days	Y	Y
	Microneedle patches	Y	$0.04\ mm^2$-$2\ cm^2$	Minimal invasion on skin	Y	Seconds	Y	Days	Y	Y
Implanted sensors	Implanted sensors	Professionals needed; pain	mm level to cm level	Infection; immune rejection	Y	Seconds	Y	Months to years	N	N

Portable devices, including disposable test strips and microfluidic chips, are made of several sensors integrated into one single device. They are user-friendly because they are easy to operate and readout results. For example, to use an early pregnancy test strip, the user simply adds drops of urine to the marked area in the test strip and checks the color changes in the sensing area after a few minutes' incubation. They can simultaneously detect multiple biomarkers on centimeter-level strips and chips without need for bulky equipment. The test strips and microfluidic chips are usually made of small amounts of reagents in cheap substrate materials (e.g., paper and plastic), making them low-cost. However, the reagents on these sensors are heavily affected by the environment (e.g., moisture and oxygen in the air), so they are usually vacuum-packed and work in a disposable manner. In addition, portable devices are difficult to achieve continuous and long-term monitoring in situ because their operations require user intervention, such as collecting samples, adding samples into inlet and reading results.

Wearable devices emerge as promising platforms for continuous and in situ health monitoring due to their easily operational, multi-functional and fully integrated features. Wearable devices can be attached to the skin surface to perform physiological monitoring, and they can be categorized into accessories-like smart devices, flexible devices, epidermal electronic sensors (E-skin) and microneedle patches. Accessories-like smart devices are the integration of advanced sensors into accessories such as watch, eyewear, wristband, *etc*. Most commercial wearable devices are accessories-like smart devices, including Apple Watch, Google Glass, Fitness Tracker, and Betwine, which have become mainstream commercial products. Flexible devices represent the dominant wearable technology, where rigid electronic components and sensing elements are integrated onto a flexible substrate to adapt to the deformation of the human skin during exercise and movement. To reduce the contact burden and enhance the attachment of sensors at the skin interface, thin, soft and breathable epidermal electronic sensors have emerged. They can fully conform to the microscopic morphology of the skin surface by directly laminating thin metal films, silicon membranes, or nanoparticle-based printable inks onto skin surface[6]. To detect biomarkers in dermal and capillaries, microneedle-based sensors have been recently developed to achieve biofluid transfer, biomarker analysis, and biotarget recognition. In a typical design of microneedle sensors, electrodes or other responsive materials are embedded at the tip of microneedles and inserted into the dermis to detect biomarkers. Wearable devices usually convert the levels of biomarkers to electrical signals, which can be repeatedly detected at high frequencies. Advances in electronic micro-nano technology have made wearable devices often small in size (~cm level) and cost effective. Besides, wearable devices are easy to encapsulate, thus minimizing environmental interference and enabling long-term in situ detection.

The implanted sensors are an inevitable trend for long-term disease monitoring because they can directly attach to internal tissues to acquire high-fidelity signals. Most of the implanted sensors seal all components in a miniaturized package and transmit data wirelessly. The dimension of clinically available sensors is at centimeter-level, which is relatively large considering that sensors are planted in vivo[7,8]. To minimize their sizes, smaller and ultrathin implanted sensors have been developed based on flexible semiconducting materials (e.g., crystalline silicon carbide nanomembranes)[9]. However, transplantation of implanted wearable devices is complicated with potential issues of infection and immune rejection, which generates large expenses and poor patient experience.

FMS TECHNOLOGIES FOR LONG-TERM DISEASE MONITORING

In the '**UMBRELLA**' standard, reliability (including high accuracy, acceptable sensitivity and good repeatability) is the most crucial factor in long-term disease monitoring since the treatment is highly dependent on the test results. Here, we choose several typical cases lasting from hours to decades, to demonstrate the FMS technologies for long-term disease monitoring.

Fever

Fever, one of the most common diseases, lasts hours to days. The deviation of a few degrees from the normal body temperature (36 °C-37.3 °C) could cause severe discomforts, irreversible impairment and even fatality to the human body[10,11]. According to different detection principles, temperature sensors are mainly divided into three categories, i.e., conductors or conductive composites-based temperature sensors, colorimetric indictors-based temperature sensors and other clinical temperature sensors (e.g., mercury and infrared thermometers) (Fig. 3). Wearable conductive composites-based (such as metal nanoparticles and carbon-based films) temperature sensors have been attached on thumb[12], upper extremity[12], underarm[13] and forehead[14], which could track temperature with small variations (<0.1 °C)[13], fast response time (within 100 ms) and wide range (from 22 to 45 °C)[15,16]. There are several potential issues associated with existing conductive composites-based temperature sensors for long-term monitoring. Firstly, due to an air gap between the sensors and the skin[14], skin surface temperature measured by sensors is usually lower than real skin surface temperature. The problem could be solved by using a thinner substrate to attach closely and conformably to the skin. For instance, Lou et al. developed an ultrathin electronic skin (e-skin) (tens of microns thick) composed of polyaniline hollow nanospheres composite films, with a high sensitivity (temperature resolution as low as 0.08 $°C^{-1}$), leading to higher detection accuracy and improved long-term wearing comfort[17]. Secondly, conductive stability faces challenges under various skin deformations, especially for thin

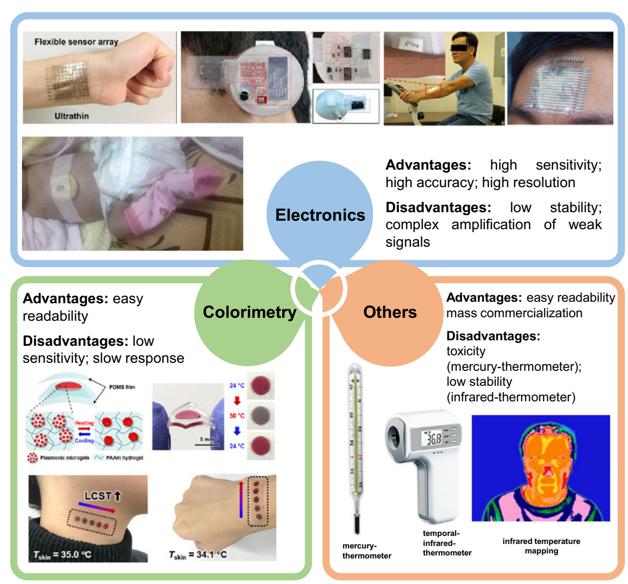

Fig. 3 Miniaturized sensor technologies for long-term monitoring of fever. Three categories of temperature sensors: electronics-based temperature sensors[14,17,18], colorimetry-based temperature sensors[19] and other temperature sensors[16] (e.g., mercury and infrared thermometers). Figure used with permission from Ren, X. et al.[14] Copyright © John Wiley and Sons, 2016. Lou, Z. et al.[17] Copyright © Elsevier, 2017. Trung, T. Q. et al.[18] Copyright © American Chemical Society, 2018. Choe, A. et al.[19] Copyright © Springer Nature, 2018. Cherenack, K.[16] Copyright © John Wiley and Sons, 2010.

sensors with a low Young's modulus. To eliminate the mechanical influences from skin deformations during temperature monitoring, a stretchable temperature sensor with a geometric engineering of the free-standing stretchable fibers (FSSFs) made of reduced graphene oxide/polyurethane composites was developed. The FSSF temperature sensor yields increased responsiveness (0.8% $°C^{-1}$), stretchability (90% strain), sensing resolution (0.1 °C), and stability in response to applied stretching (±0.37 °C for strains ranging from 0 to 50%)[18]. Conductive composites-based temperature sensors are potential tools to monitor fever due to their high sensitivity and fast response time. However, complex external circuits (*e.g.*, amplifying circuits) and functional deterioration caused by various external stimuli (e.g., sweat and skin deformations) limit its application during long-term temperature monitoring.

To solve this problem, colorimetric temperature sensors have been developed as commercial products for several years due to their easy readability by naked eyes, relatively low cost and easy operation. The composition of the colorimetric temperature sensor is simple, consisting of temperature-sensitive discoloration materials encapsulated in a waterproof layer. There is no risk of circuit corrosion. Besides, one area of the colorimetric sensor corroded by sweat will not affect the color rendering of other areas. Although it has slower response time (several minutes) and lower resolution (0.5–1 °C)[19], most colorimetric sensors from literature and markets can meet the demands of fever monitoring at home. Clinically, mercury thermometers and infrared thermometers are commonly seen for temperature sensing. In a mercury thermometer, the mercury expands and contracts with temperature changes, thus the temperature can be read from the scale. It exhibits good stability, high sensitivity, good repeatability, good durability and power-free property. An infrared thermometer converts the energy absorbed into an electrical signal, achieving distant temperature measurements and avoiding virus cross-infection. Thus, an infrared thermometer is easy to achieve large group detections. Most commercial products and research prototypes of temperature sensors can realize reliable long-term monitoring for fever (hours to days) (Fig. 2), because of simple detection principles, mature technologies and advanced thermal responsive materials.

Wound

Wound healing is a dynamic process, which totally lasts from days to months[20]. The inflammation phase lasts about 2~5 days after injury, and then new tissues begin to form in 2~10 days and tissue remodeling begins and lasts over months or years[21]. Studies in wound monitoring mainly focus on different sensing signals according to the time after injury and the wound phases. For example, in inflammation phase, bacteria and inflammatory factors are the main monitoring signals[22]. In tissue formation phase, researchers and clinicians focus on collagen (the constituent of extracellular matrix), oxygen and humidity (important factors of neovascularization)[23–29], while the force on and around the wound surface is the primary signal in the phase of wound closure. Zhu et al. put pH indicating dye and glucose-sensing enzyme into the super-hydrophilic zwitterionic hydrogel matrix, which could avoid the interference with hydrophobic active sites of the enzyme due to its high hydrophilicity[23]. The device can monitor pH and glucose in wound exudate for 14 days in vivo with a resolution of 0.5 and pH range of 4–9. To prolong the monitoring duration, Boesel et al. reported a fluorescent-based sensor to monitor the concentration of two wound-related fluctuating biomarkers (i.e., glucose and pH). This sensor can monitor biomarkers for more than 30 days because it is based on a pH-sensitive fluorometric dye (hydroxypyrene-1,3,6-trisulfonic-pyranine-benzalkonium), which is more stable than traditional fluorometric dyes on the wound because of its resistance to

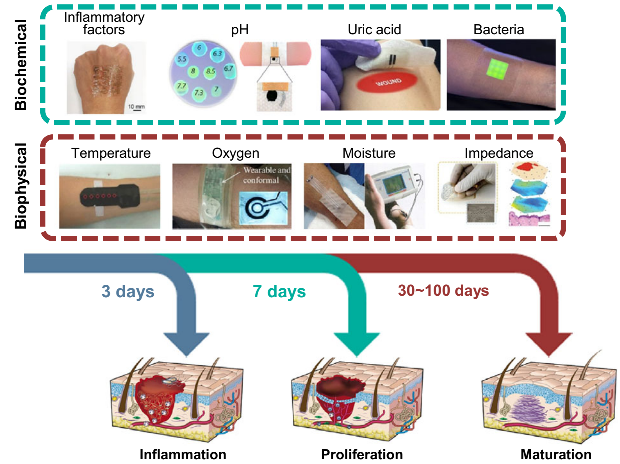

Fig. 4 Miniaturized sensor technologies for long-term monitoring of skin wound. The wound healing process can be divided into three stages: inflammation phase (lasting for about three days), proliferation phase (lasing for about a week) and maturation phase (lasing for about several months). During the wound healing process, biochemical signals (including uric acid[28], bacteria[22] and pH[94]) and biophysical signals (including temperature[24], oxygen[27], moisture[25] and impedance[26]) can be monitored. Figure used with permission from Kim, J. et al.[28] Copyright © Elsevier, 2015. Thet, N. T. et al.[22] Copyright © American Chemical Society, 2016. Tamayol, A. et al.[94] Copyright © John Wiley and Sons, 2016. Zhang, Y. et al.[24] Copyright © John Wiley and Sons, 2016. Li, Z. et al.[27] Copyright © The Optical Society, 2014. Milne, S. D. et al.[25] Copyright © John Wiley and Sons, 2016. Swisher, S. L. et al.[26] Copyright © Springer Nature, 2015.

hydrolysis[30]. Besides, the integrated smart bandages have also been developed along with the development of flexible electronics, enabling a feedback system (status including monitoring and treatment) capable of real-time indicating wound. For example, Ali et al. designed a smart bandage realizing pH and temperature monitoring, and on-demand drug delivery[31]. The smart bandage includes pH sensor, temperature sensor and stimuli-responsive drug releasing system, showing stability for at least 5 h in vitro due to the thermo-responsive hydrogel drug carrier. Besides, to improve the wearing comfort of smart bandages, a flexible and breathable nanomesh substrate encapsulated with thermo-responsive drug-laden hydrogel was used to replace conventional plastic substrate[32]. The device realizes real-time temperature monitoring at the wound site and effective anti-infection therapy, showing great potential for wound care. For commercially available products, DermaTrax is popular in the markets, which contains temperature, moisture and pH sensors, realizing remote monitoring of the wound condition, as well as the state (e.g., humidity) of the dressing itself. Then the data can be transmitted to nurses' stations wirelessly, helping doctors to make decisions (Fig. 4).

The drastically increasing demand for wound care will boost the development of long-term wound monitoring technology in the future. For developing materials and technologies for long-term wound monitoring, important characteristics of wound monitoring should be considered. Most importantly, the wound interface is wet (filled with fluid) and soft. So wet adhesion property and biocompatibility of materials for smart bandages should be considered. In addition, the timescale of wound healing in diverse wound types varies. For example, for a burn wound, the infection takes place from 48 h to a week after burn, while for a diabetes foot wound, ulcer wound infection would occur at any stage of wound healing. Thus, specific timescale needs to be covered for wound monitoring sensors. Existing sensors for wound monitoring have a duration of several days to a month, which are appropriate

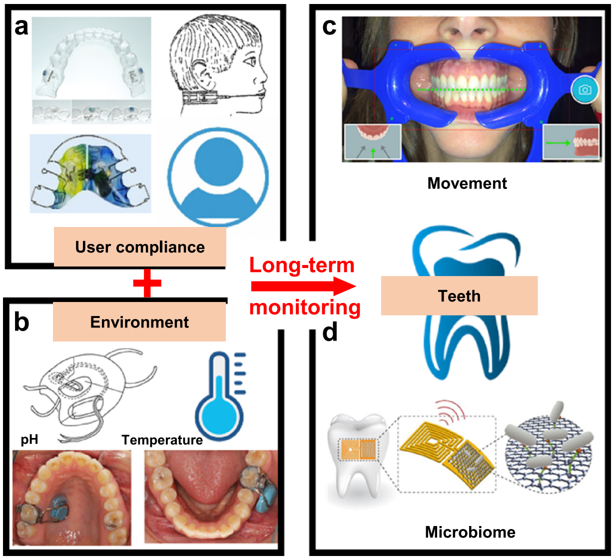

Fig. 5 Miniaturized sensor technologies for long-term monitoring of orthodontics. a Monitoring the compliance of wearing dental braces based on the degree of pigment diffusion from polymer pores and force required for orthodontics[33,36]. **b** Wearable devices to monitor pH and temperature of saliva[38]. **c** Judging the movement of teeth based on photos taken by smartphones[95]. **d** Wearable patch attached onto teeth to detect oral microbiomes[37]. Figure used with permission from Schott, T. C. et al.[33] Copyright © Allen Press Inc, 2011. Kyriacou, P. A. et al.[36] Copyright © Springer Berlin Heidelberg, 1997. Igarashi, K. et al.[38] Copyright © Elsevier, 1981. Hansa, I. et al.[95] Copyright © W.B. Saunders Ltd, 2018. Mannoor, M. S. et al.[37] Copyright © Springer Nature, 2012.

for acute wounds (days to weeks). However, they are not sufficient for chronic wounds (e.g., diabetic foot wound), which lasts for months to years (Fig. 2).

Orthodontics

Orthodontics is a branch of dentistry, specializing in correcting teeth and jaws that are not in the right position. To perform better orthodontics, various sensors have been developed to monitor patient compliance, oral hygiene, load force on teeth and teeth movement (Fig. 5). Patients' compliance is prerequisite to guarantee the effective treatment of orthodontic appliance. A commercially available dyed blue dot as a wear-compliance indicator of the Invisalign Teen ® System can evaluate the compliance for about 2 weeks through polymer-coated dye fading in oral aqueous solutions with wearing duration[33,34]. However, colorimetric compliance indicators are easily affected by simple intentional or unintentional manipulations, for instance, oral pH value, temperature, drinking water or soft drinks. To address this, electronic microsensors have been developed. TheraMon® microsensor is a clinically and practically feasible sensor used to continuously monitor wearing duration through measuring temperature for two weeks and wirelessly transmitting the data through Bluetooth[35]. Besides, digital timers, digital counter/memory circuits and force sensors have been used to measure compliance[36]. The oral environment affects both teeth health and results of orthodontic treatment. To detect the oral microbial environment during orthodontics, Mannoor et al. printed graphene onto tooth enamel to form a bio-interfaced platform, which achieves the detection of bacteria at single-cell levels[37]. Since plaque pH measurement has been widely used to evaluate cariogenic potential, a transistor-based pH electrode covered with silicon nitride, has been integrated into a small chip and worn in the oral cavity to detect pH continuously for 40 min, with a resolution of 0.2[38]. The results of orthodontic treatment and movement of teeth can be measured by taking photos using a smartphone with a movement tracking algorithm. It is a convenient and low-cost system to realize remote monitoring for orthodontic patients, which maintains excellent teeth care[39]. However, detection of movement of teeth by taking photos is discontinuous, and a device that can meet the needs of long-term continuous detection of teeth movement has not yet to be developed.

Today, most orthodontic treatments are observed visually and judged by doctors based on their experience, which makes the treatment lack accuracy and puts the teeth at risk. FMS to monitor teeth condition can be integrated with a reminder system to reduce the risk of injury and shorten treatment duration. However, the average orthodontic treatment duration requires to be 14 to 24 months, while the miniaturized sensors both used in the clinic and developed in the lab can only monitor for a maximum of two weeks. There is a huge gap between the existing sensors and the practical demands for long-term orthodontics monitoring (Fig. 2).

Diabetes

Diabetes is a defect in processing glucose from food and making glucose power the tissues of the body. Diabetes requires monitoring throughout life to mitigate the harm caused by disease. Clinical Practice Guidelines for Diabetes Management[40] recommend that patients should monitor their glucose levels 6–8 times every day. Colorimetric methods have been used to discontinuously detect glucose levels. For instance, Koh et al. embedded chemical analytes responsive in a colorimetric fashion in a wearable epidermal biosensor (a disk patch with a diameter of 3 cm and thickness of ~700 μm) to detect glucose level in sweat, where near field communication (NFC) was used to transfer captured images for quantification of glucose levels. The limit of detection of glucose is 200 μM over a range of 0–25 mM[41]. Yetisen et al. injected colorimetric agents into the dermis to form a dermal tattoo biosensor to detect glucose concentration (0 to 50 mM) in skin interstitial fluid (ISF) with the resolution of 2 mM[42]. In the dermal glucose sensor, D-glucose is oxidized to D-gluconolactone by the catalysis of glucose oxidase, forming hydrogen peroxide (H_2O_2), that enzymatically oxidizes 3,3′,5,5′-tetramethylbenzidine (TMB), showing green colors[43]. However, the color response of TMB is irreversible and thus the sensor can only provide one-time detection.

To realize continuous monitoring of glucose, integrated wearable devices have been developed to monitor sweat glucose in a real-time manner using the electrochemical method[44–46]. However, this sensor is not suitable for the sedentary group because of less sweating. To address this, Emaminejad et al. integrated electrochemical iontophoresis in a wearable sweat analysis platform (the size of wristbands with a 100-μm-thick substrate) to induce sweat for real-time sweat glucose analysis with the help of pilocarpine (a sweat gland stimulator) loaded in a hydrogel carrier[47]. This enhanced iontophoresis opens up the possibility for sweat glucose monitoring of the sedentary group. It can monitor sweat glucose for duration of an entire exercise (20~100 min) with a typical sweat glucose concentration range from 0 to 100 μM and the sensitivity is 2.1 nA μM^{-1}. For longer glucose monitoring, skin ISF is an ideal sample source, because it is formed by capillary filtration of blood and its glucose concentration is almost the same as that in blood[48]. Microneedle-based electrochemical biosensors have been developed to monitor dermal glucose in skin ISF with minimal invasion. These sensors (the overall area of the sensing portion is about 0.04 mm^2–0.4 mm^2) have microneedle electrodes modified with glucose oxidase to dynamically measure glucose concentrations in skin ISF from hours to weeks[49,50], with sensitivity 1.51 nA mM^{-1}, ranging from 0 to 200 mg dL^{-1}. Compared with minimal-invasive detection using microneedles, non-invasive continuous detection

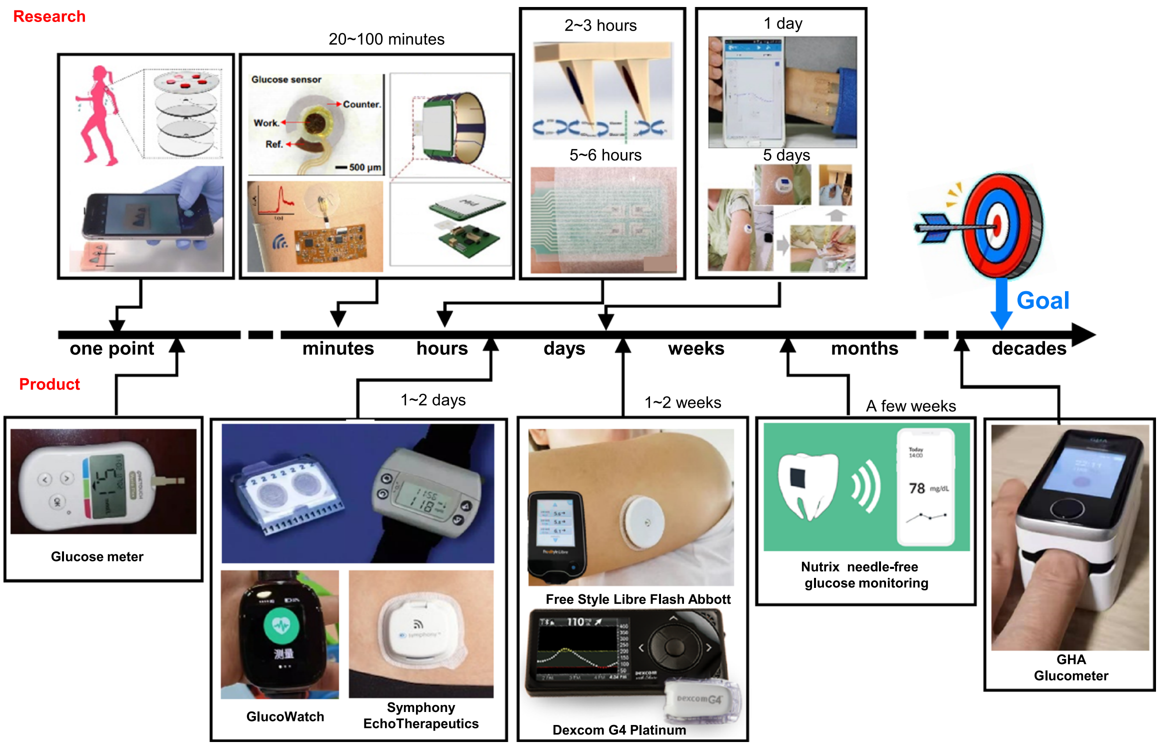

Fig. 6 Miniaturized sensor technologies for long-term monitoring of diabetes. Research advances in glucose sensors for one-point detection[42,96], and continuous monitoring for minutes to days[44–46]. Commercially available glucose sensing devices for one-point detection and continuous monitoring for days to months[37,38]. Figure used with permission from Yetisen, A. K. et al.[42] Copyright © John Wiley and Sons, 2019. Xiao, J. et al.[96] Copyright © American Chemical Society, 2019. Kim, K. B. et al.[44] Copyright © Elsevier, 2019. Lee, H. et al.[45] Copyright © Springer Nature, 2016. Martin, A. et al.[46] Copyright © American Chemical Society, 2017. Mannoor, M. S. et al.[37] Copyright © Springer Nature, 2012. Igarashi, K. et al.[38] Copyright © Elsevier, 1981.

has greater application potential. Chen et al. integrated a skin-like electrochemical biosensor with twin channels, forming an ultrathin (~3 μm) nanostructured biosensor, to accurately monitor glucose in skin surface through transporting intravascular blood glucose to the skin surface in a noninvasive way with high sensitivity (130.4 μA mM^{-1})[51]. Lipani et al. developed a graphene-based platform (the size of cm level), which detects glucose from skin ISF through electroosmotic extraction to realize noninvasive and continuous glucose monitoring for more than 4 h with a sensitivity of ~2.2 μA mM^{-1} cm^{-2} with a limit of detection of 2.8 μM[52] (Fig. 6).

An increasing number of commercial products have become available to provide glucose monitoring in longer periods than academic researches (Fig. 6). The fingertip blood-based glucose meter is the commonly used commercial sensor. Although it is low-cost and highly reliable, it is associated with the issues of incapability for continuous detection, pain and risk of infection. The first GlucoWatch was launched in 2002, and it applies a low electric current to the skin to extract glucose out of skin surface with minimal invasion every 10 min. Patients can build in an alarm program to alert dangerous hyperglycemia or hypoglycemia. The sensor can work spans from 12–48 h. For longer glucose monitoring, a generation of glucose monitors has been developed, e.g., wearable flash glucose monitor. Freestyle Libre is reported to be able to continuously measure the glucose level in the skin ISF for ~14 days without the need for calibration. Although there exists a delay when measuring glucose in skin ISF, especially after meals and exercise, patients can track glucose trends and take intervention earlier. Nutrix is an invisible, non-invasive, and patient-friendly nanosensor placed on the tooth for detecting glucose level in the saliva for a few weeks, where the readout is transmitted to an external App in a mobile phone. It can also monitor food intake and provide valuable information for patients and doctors. Diabetes is a lifelong disease that requires lifelong monitoring once diagnosed (lasting for decades). However, almost all miniaturized sensors only monitor for a few weeks, which cannot achieve long-term monitoring for diabetes (Fig. 2).

FMS TECHNOLOGIES FOR MONITORING OF INVIGORATING AND DEBILITATING FACTORS

Monitoring of factors that affect an individual's health is also an important application of this class of technologies. Such factors can include exercise (minutes to hours), alcohol consumption (hours to days), and smoking (months to decades). In the '**UMBRELLA**' standard, being user-friendly, especially non-invasive, is the most important factor during long-term health monitoring.

Exercise

Doing exercise is the most common way to keep healthy and active and exercise usually lasts from tens of minutes to hours. Most of the reported exercise monitoring methods and platforms can meet the requirements of monitoring duration. Movement sensors, such as accelerometers/gyroscopes, pedometers, and positioning systems, are commonly used to estimate sports load, which are convenient and reliable for tracking player's performance during long-term sport monitoring[53,54]. Particularly, kinematic variables (e.g., distance and average velocity) are highly relevant to health situations of players, reflecting the energy consumption during sports[55,56]. Physiological signals (e.g., heart rate, sweat loss, respiratory and electrical signals) during exercise have been widely monitored by commercialized platforms. Heart rate is an essential signal indicating sports intensity and physiological adaptation. At present, emerging commercially

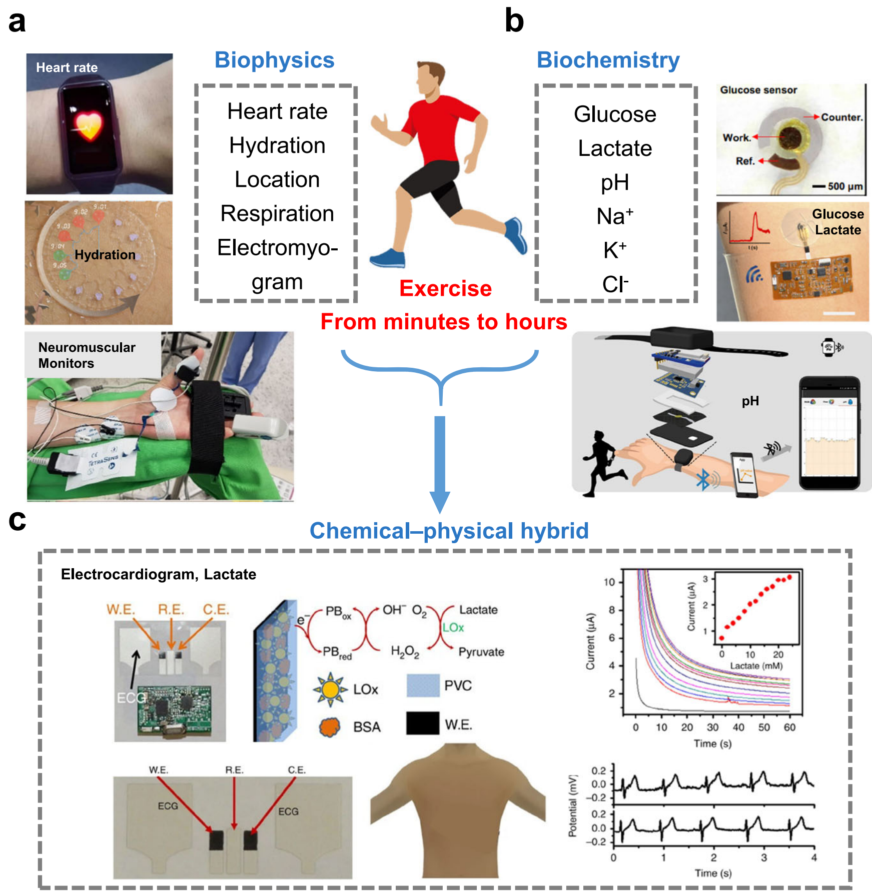

Fig. 7 **Miniaturized sensor technologies for long-term monitoring of exercise.** Health monitoring during exercise often lasts for minutes to hours. **a** Biophysical indicators for exercise monitoring commonly include heart rate, sweat loss, location, pace and respiration[97]. **b** Biochemical markers for exercise monitoring commonly include glucose, lactate, pH, and ions[44,46,59]. **c** Chemical-physicl hybrid health monitoring devices used to detect both physical signal and biochemical biomarkers (e.g., lactate)[60]. Figure used with permission from Choi, J. et al.[97] Copyright © John Wiley and Sons, 2017. Kim, K. B. et al.[44] Copyright © Elsevier, 2019. Martin, A. et al.[46] Copyright © American Chemical Society, 2017. Bandodkar, A. J. et al.[59] Copyright © Elsevier, 2014. Imani, S. et al.[45] Copyright © Springer Nature, 2016.

available heart rate monitors have realized direct heart rate monitoring in the wrists or fingertips using optical sensors (e.g., wrist bands or smartphones).

Quantitative analysis of physiological signals (e.g., sweat loss) and biochemical signals (e.g., glucose, lactic acid, pH, and electrolytes) is of great significance for health status monitoring, which can reflect the physical state and the metabolism in the body. Koh et al. designed a soft, flexible, and stretchable microfluidic system to continuously measure the sweat loss for 60 min, achieving longer-term sweat loss monitoring by adjusting the length and width of the channel, and the size of the sweat inlet[41]. Sweat generated during exercise is the main sample source for the detection of biochemical signals during exercise. Koh et al. embedded chemical sensing elements in a colorimetric manner to multiple biomarkers (i.e., glucose, lactate, chloride and hydronium ions) in a wearable microfluidic device[41], realizing the simultaneous detection of multiple targets (limit of detection of glucose: 200 μM over a range of 0–25 mM). Besides, Curto et al. developed a microfluidic platform, where fresh sweat continuously flows through the sensing channels, achieving continuous and real-time analysis of biomarkers in sweat[57]. For these techniques, the colorimetric platforms can semi-quantitatively detect biomarkers in sweat, while electrochemical-based detection platforms can accurately quantify multiple biomarkers in sweat. For instance, Kim et al. presented a wearable and integrated electrochemical sensor platform to simultaneously and continuously track multiple biomarkers in sweat during exercise[44]. Bandodkar et al. embedded galvanic cells within a flexible sensor to form a sweat-activated 'stopwatch', which can record real-time information of discrete microliter volumes of sweat, precisely measuring the dynamic and fluctuated composition in sweat in situ[58]. Due to higher levels of thinness and gas permeability, tattoo-like sensors are also developed to detect biomarkers in sweat[59]. However, there is a lag during monitoring metabolites in sweat since the biomarkers in blood diffuse to ISF and then go into the sweat glands by capillary filtration. As more sweat is produced by the sweat gland, which pushes the biomarker to the skin surface, taking tens of minutes. Sweat-to-blood lag may also lead to inaccurate monitoring. To address this, some researchers have combined physiological and biochemical signals to evaluate the physical status of players more accurately. For instance, Imani et al. introduced a wearable, flexible and multi-functional sensor, which can simultaneously and real-time monitor a biochemical target (e.g., lactate) and a physical signal (e.g., electrocardiogram (ECG)) with negligible cross-talk[60] (Fig. 7).

However, affected by the environment and sweat-to-blood lag in metabolism, the current results of exercise monitoring face challenges in obtaining highly reliable and repeatable results. In the future, more advanced technologies should be developed for exercise monitoring to realize accurate and timely detection. Besides, alternative sample sources should also be explored to circumvent the lag between sweat and blood during exercise monitoring.

Alcohol

Alcohol affects all parts of the body, especially when the organs are exposed to blood with a high concentration of alcohol for a long term. Alcohol could be monitored in various body fluids, such as blood, urine, saliva[61,62], breath[63], ISF[64–66], and sweat[65,67]. Currently, blood alcohol concentration and breath alcohol concentration are the most commonly used indicators of alcohol intoxication. Blood alcohol measurement is the most accurate, but it cannot realize real-time and in situ monitoring due to the invasive sample collection, complicated operation, and single detection. Breath alcohol, which can be easily detected by a breathalyzer, is widely used to estimate blood alcohol due to their strong correlation. However, due to many external factors which may influence a preliminary reading (such as mouthwash and environmental contamination), the breathalyzer might generate false results. As an alternative sample source to blood and breath alcohol analysis, sweat has the potential to realize non-invasive and real-time monitoring of alcohol concentration. Two wearable biosensors (Giner WrisTAS and SCRAM)[68] have been developed to monitor alcohol in sweat for 3 weeks with 1 min intervals and 6 months with 30 min intervals. But there is a delay of 0.5 to 2 h compared to blood alcohol concentration because it takes time to generate sweat. To address this, the iontophoretic biosensing system is developed to reduce the delay by stimulating sweat generation. For instance, Kim et al. integrated flexible biosensing systems with iontophoresis and Bluetooth communication, realizing in-situ and real-time alcohol monitoring in sweat with a high sensitivity (0.362 ± 0.009 μA mM^{-1}) in the range of 0 to 36 mM[67]. Hair et al. developed a simple sensing system to monitor alcohol, presenting visible color by a series of enzymatic reactions with the low limit of detection (0.0378 mM) in the range of 0 to 54.23 mM, which has the potential to realize long-term alcohol monitoring[69]. During drinking, alcohol is absorbed within 5 to 10 min, showing peaks in the blood 30 to 90 min after drinking and lasting for 12 h[70,71]. Alcohol in sweat lasts up to 24 h and for 24 to 48 h in saliva[48]. About 10% of alcohol leaves the body through the urine, which lasts for three to five days[48,72,73]. Some commercial sensors mentioned above have been able to monitor alcohol for months and are suitable for long-term alcohol monitoring (Fig. 2).

Smoking

Smoking can cause serious damage to health, especially lung-related chronic diseases[74,75]. Smoking monitoring devices can be divided into two categories according to the process of smoking[76]. One is for monitoring smoking behavior, which indicates whether user smokes or not, mainly by levels of nicotine and carbon monoxide and hand gestures[77]. For example, CoVita developed a breath monitor to help people quit smoking, which mainly monitors carbon monoxide levels by breath analysis sensors and then transports data by connecting to a phone. IntelliQuit developed a series of Cloud-based nicotine testing devices for all tobacco users, which could quantify nicotine consumption from 'Heat-not-burn' tobacco products (e-cigarettes that are heated, rather than being burned, to generate vaporized nicotine at relatively low temperatures). Besides, there are many reports about smoking monitoring via detecting hand gestures. For instance, Sazonov et al. designed a wearable sensor to monitor the distance between hand and mouth during smoking[78]. By recognizing hand-to-mouth gestures, the sensor could provide detailed information on smoking behaviors and help to analyze behavior patterns during smoking.

The other category focuses on the effects on health after smoking, usually through monitoring physiological signals such as heart rate and blood pressure for a long time[79]. For example, AliveCor developed a tiny, rectangular device named 'KardiaMobile' for heart rhythm monitoring. Its procedure is so simple that you just need to put fingers on the pads of the device, and ECG signals could be acquired after a few seconds. Most smoking sensors reported could only work for several hours to days, but smoking is a long-term process that requires monitoring for years and even decades (Fig. 2). Therefore, smoking monitoring devices with a prolonged timescale should be developed in the future. Besides, more relevant smoking indicators need to be explored to assess the effects of smoking more accurately.

RATIONAL SAMPLE SOURCES OF FMS

Collecting sample is the first step in health monitoring. For selecting proper sample sources in long-term monitoring, continuity, invasiveness, lag time and user comfort are the mostly highlighted parameters for considerations in a rational sensor design. Blood is believed to be the gold-standard biofluid sample for disease diagnostics, but detecting biomarkers from the blood sample in a continuous manner remains an unsolved challenge, mainly due to the invasiveness of the blood sampling process, which induces discomfort and potential infection to patients, and further contributes to declined compliance. Therefore, blood sample is ideal for short-period applications (i.e., no more than several days) where biomarkers need to be accurately measured to perform reliable diagnosis of chronic diseases. Urine is also a commonly used sample source for clinical detection, due to its appealing features like non-invasive access, large sample volume, and abundance of health-related biomarkers. However, the composition and concentration of health-related biomarkers in urine significantly differ from those in the blood due to the filtration of kidney, resulting in lost or weakened physiological signals, and increased interference noise. So, small molecules in urine, which can filter through the kidney (e.g., glucose, pH, ketone and nitrite), are promising possibilities to qualitatively monitor chronic diseases in low frequency. Sweat can be easily accessed in a noninvasive way. However, concentrations of sweat biomarkers (e.g., glucose) could be much lower than those in blood and a metabolic lag between sweat and blood cannot be ignored. Additionally, uncontrolled sweat flow, evaporation and contamination issues may cause lowered accuracy of the sensing. Sweat sensors can find uses for continuous sensing of metabolites and dehydration during exercise or diagnosis for secretory dysfunction of epithelial cells (i.e., cystic fibrosis).

Tear, skin ISF, and saliva can achieve continuous long-term health monitoring. The biomarkers in tears can reveal useful information on systemic disorders and ocular conditions. However, normal contact lenses are recommended to wear for no more than 12 h and take off during sleeping to avoid potential eye diseases, thus limiting the tears used in long-term monitoring. Therefore, it is promising to sense biomarkers in tears to continuously monitor biomarkers during daytime. Skin ISF can be obtained in a non- or minimally invasive way by electrically stimulating or physically puncturing the stratum corneum. However, collecting skin ISF is more difficult than other biofluids, so it is more suitable to implant the sensors under the skin to continuously monitor the biomarkers in skin ISF. Saliva sensing is non-invasive and can continuously monitor biomarkers in saliva. The challenges of saliva-based sensors mainly involve difficulties in miniaturization, encapsulation, battery life extension, and data transmission. In addition, maintaining device stability under issues like the humid oral environment, relatively enclosed cave and frequent movements caused by talking and chewing sets another hurdle for saliva sensing. Till now, saliva has been used to detect biochemical cues in the oral environment, including oral microbes, pH and mucosal secretions, especially in orthodontics treatment.

Exhaled breath sensors are usually integrated into a mask or stuck on the nostril, which is easy and comfortable to wear. However, the relationship between volatile biomarkers and diseases is unclear, which hinders the application of exhaled breath-based sensors in disease monitoring. Compared with biomarkers in blood, concentrations of the volatile biomarkers are relatively low, so sensors are required to be extremely sensitive. Typical applications of breath sensors include evaluations of chronic respiratory disease and volatile biomarkers (e.g., smoking and alcohol) via continuously monitoring breath rate.

CONCLUSION AND PERSPECTIVES

In this review, we introduce the recent advances in FMS technologies for long-term monitoring of diseases and health factors. Then selection guidelines from perspectives of sample sources and detection methods for the rational design of FMS for long-term physiological monitoring are summarized. This review highlights the monitoring duration for specific sensing tasks, which are important for physiological monitoring in the long term.

Although significant progress has been made in FMS technologies for long-term physiological monitoring, there are some key challenges and technological gaps to be addressed to realize the full potential of long-term monitoring devices. One major challenge is to develop responsive materials with improved efficiency and stability in long term, to overcome the existing conundrum induced by shortcomings of currently available materials (e.g., irreversible, unstable and easily polluted). A new generation of synthetic biomaterials may promise possibilities to solve the issue. For instance, living cells can adjust their behaviors dynamically in biochemical or biomechanical ways in response to the changes of health-related signals (*e.g.*, nutrient levels, body temperature, water content, and electrical pulses). The changed behaviors of living cells can be captured by external devices and reflect body conditions[80–82]. Another challenge is the low capacitance of existing power sources integrated into the FMS. The strategies are to produce miniaturized sensing devices with lower power consumption[83] and develop self-powered devices, such as harvesting energy from the body movement[84–86]. In addition, energy sources available from the surrounding environment, including sunlight, thermo, and electromagnetic energy[87], can produce a high power density of tens of mW cm^{-2}[88]. During long-term service, sensing devices may face complex and changing conditions in outdoor situations that are different from the lab environment, bring special demands for long-term physiological monitoring[89]. Actually, all components of monitoring devices (i.e., substrates, sensing elements, power supply modules, and encapsulating materials) face challenges in such varying conditions. For instance, it is challenging for substrates to keep flexible and stretchable at subzero temperatures, high temperatures or dry conditions. It is necessary for sensing elements to keep intact under large deformations during body movement and maintain adhesion in highly hydrated conditions. Therefore, a new generation of materials and structures should be designed to provide opportunities for long-term monitoring devices in multiple environmental conditions[90–93].

To sum up, with the upgraded technology and development of sensors and methods for long-term physiological monitoring, it is believed that physiological information collected using miniaturized sensors will help to improve civil quality and make the world better.

DATA AVAILABILITY

The data that support the findings of this study are available within the paper or available from the corresponding author upon reasonable request. Moreover, sources of all the figures are provided with the paper.

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AUTHOR CONTRIBUTIONS

R.H. and H.L. contributed equally to this work. R.H. and H.L. wrote the manuscript under the supervision of F.X. Y.N. prepared Figs. 4, 5. H.Z. prepared Table 1. G.G. revised the manuscript. All authors reviewed the manuscript and provided corrections and comments.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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