Non-invasive Flexible and Stretchable Wearable Sensors with Nano-based Enhancement for Chronic Disease Care

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Abstract—Advances have been made in flexible and stretchable electronics, functional nanomaterials, and micro/nano-manufacturing in recent years. These advances have accelerated the development of wearable sensors. Wearable sensors with excellent flexibility, stretchability, durability and sensitivity, show attractive application prospects in the next generation of personal devices for chronic disease care. Flexible and stretchable wearable sensors play an important role in endowing chronic disease care systems with the capability of long-term and real-time tracking of biomedical signals. These signals are closely associated with human body chronic conditions, such as heart rate, wrist/neck pulse, blood pressure, body temperature and biofluids information. Monitoring these signals with wearable sensors provides a convenient and non-invasive way for chronic disease diagnoses and health monitoring. In this review, the applications of wearable sensors in chronic disease care are introduced. In addition, this review exploits a comprehensive investigation onto requirements for flexibility and stretchability, and methods of nano-based enhancement. Furthermore, recent progress in wearable sensors including pressure, strain, electro-physiological, electrochemical, temperature and multi-functional sensors, are presented. Finally, opening research challenges and future directions of flexible and stretchable sensors are discussed.

Index Terms—Non-invasive wearable sensors, flexible and stretchable electronics, nanotechnology, chronic disease care

I. INTRODUCTION

CHRONIC DISEASE requires a continuing medical care and limits the daily activities of patients. This health problem is caused by the destructive behaviors (e.g., tobacco, lack of exercise, and irregular diet) of the individuals. In addition, the aggravating global and regional problems such as population aging, environmental pollution, and food safety have been some of the major inducements of chronic disease. Since chronic diseases are difficult to be perceived, it is not possible for patients to detect their true health condition until the symptoms are severe enough to be recognized. Also, patients suffering from chronic diseases need to go to the hospital frequently and spend a lot of money for medical treatment. The early detection of a chronic disease is an emerging vision of getting primary prevention using wearable devices to continuously monitor the physiological conditions of the healthy states. Wearable device provides a new way to change the traditional chronic disease care towards continuous and mobile health monitoring. It is not only used to measure the various biomedical characteristics, such as blood pressure, body temperature, electrophysiological signals, heart rate, and blood glucose, but also to monitor the body motion information, such as muscle movement, joint angle, and gait. Available electrophysiological signals are electrocardiograph (ECG), electroencephalograph (EEG), electromyography (EMG) and electrooculogram (EOG). The trends of signals being monitored by wearable devices might provide patients with an indispensable and very important indication of the potential risks of chronic disease. It can be foreseen that wearable technology, as a new clinical method and medical instrument with the features of remote and timely diagnoses, will be wildly investigated and applied in chronic disease care.

The recent advances in flexible and stretchable electronics [1], wireless communications, nanotechnology [2] and sensor technologies [3], have triggered more and more significant technological progress in advanced wearable devices. Flexible and stretchable electronics enables wearable devices to be integrated with arbitrary curved surfaces while maintaining the performance and reliability of the devices. Non-invasive wearable devices for chronic disease care have particularly
benefitted from such technological evolutions. As an important part of wearable devices for the accurate diagnosis of chronic diseases, versatile wearable sensors have been attracting more and more attention. Early wearable sensors are inconvenient to wear and carry due to the limitations of electronic technology and material science, mainly with a larger structure [4], as shown in Fig. 1(d). Today’s wearable sensors have the compact size and are commonly integrated in consumer electronics, such as watches, wristbands, armbands, glasses or helmets [Fig. 1(c)]. They can connect to mobile terminals via Bluetooth or wireless networks [5]. Through the applications installed in these mobile terminals, wearable sensors can record, upload and analyze health data. Most wearable watches are based on optoelectronic components because of their miniaturized size, electromagnetic immunity and less susceptibility to harsh environments [6]. However, most of the watch-like wearable sensors are based on a rigid substrate. The sensors need to be embedded in a rigid package [7] and has a mechanical mismatch with human body, which affect their comfort level and measurement results. The improved technology uses the flexible conductors connected to rigid distributed circuits to achieve the requirement for flexibility, also called heterogeneous integration technology [Fig. 1(b)]. Nevertheless, heterogeneous sensors still cannot achieve random tension, bending and torsion and other special forms, which does not conform to the skin, greatly limiting the stability and accuracy of the measurement [8]. By contrast, intrinsically soft materials are attracting more and more attention owing to their mechanical flexibility and stretchability [9]. The advanced wearable sensors based on soft materials can be integrated on the human skin surface with similar mechanical properties to the skin and can follow the skin movement together, so-called epidermal sensor [10]. Epidermal sensor and electronic skin (E-skin), as well as electronic tattoo (E-tattoo), are similar concept [11], which get rid of the shackles of physical accessories. These sensors can be attached to the skin by reversible paste, even no paste, enabling the measurement of any location [Fig. 1(a)]. Based on these advanced wearable sensors that addresses the challenges in comfortability, traditional centralized healthcare services are undergoing a process of changing towards a new method for chronic disease care, which is accessible to patients at all times [12], [13]. Since most nanomaterials are capable of offering sensing function and mechanical flexibility and stretchability, wearable sensors with nano-based enhancement show great performances to satisfy the requirements for chronic disease care [14]. The development of nano-based wearable sensor accelerates their applications in long-term chronic disease care. Numerous nanotechnologies have attracted the attention of many researchers to develop advanced wearable sensors for chronic disease care. Hence, non-invasive flexible and stretchable wearable sensor with nano-based enhancement becomes a new frontier in the field of mobile healthcare, especially for chronic disease care.

However, many challenges/gaps of existing research efforts are in the way of applying flexible and stretchable wearable sensors to clinical conditions. For example, the motion artifacts have an influence on the signal quality of the pressure sensor. Most existing strain sensors cannot simultaneously achieve high sensitivity and high stretchability. Most studies of electrophysiological sensors were fabricated by mixing conductive nanomaterials with an elastic polymer resulting in the degradation of signal quality over the time. Current electro-
chemical sensors only detect one analyte in body fluids or breathe gas. The accuracy of wearable temperature sensors needs to be enhanced to satisfy the requirement for chronic disease diagnosis. In addition to the characteristics of wearable sensor, advanced manufacturing methods and novel functional materials need to be further developed to enable wearable sensors to be applied in chronic disease care.

The goal of this review is quadripartite: 1) to exploit a comprehensive investigation into the advancement of flexible and stretchable wearable sensors with nano-based enhancement for chronic disease care; 2) to summarize the requirements of wearable sensors for clinical application and the methods of nano-based enhancement for flexibility and stretchability; 3) to identify the gap between state-of-the-art research and healthcare demands; 4) to envision the scientific challenges of wearable sensors and the directions for future research.

As shown in Fig. 2, this review starts at an overview of applications in chronic disease care in Section II. Following that, the requirements of wearable sensors will be summarized in Section III. In addition, the nano-based enhancement for flexibility and stretchability of wearable sensors will be presented in Section IV. Moreover, state of the art of wearable sensors with nano-based enhancement will be presented in Section V. Furthermore, the challenges and directions of wearable sensors will be analyzed in Section VI. Finally, the conclusion and future perspectives will be briefly discussed in Section VII.

II. APPLICATIONS IN CHRONIC DISEASE CARE

The combination of miniaturized wearable sensors, signal processing, power supply, and wireless communication provide patients with more personalized treatment and enable doctors to monitor patients during their daily routine in a real-time manner. Long-term and continuous monitoring of patients helps to adjust treatment timely and to achieve accurate and quantified treatment. Wearable sensors provide data support for the research and traceability of ever-increasing chronic diseases. The various chronic diseases, such as chronic respiratory diseases [15]–[17], diabetes [18], congestive heart failure [19], [20], Parkinson’s disease [21], [22], osteoarthritis [23] and hypertension [24], [25], have been monitored by different types of wearable sensors, as shown in Fig. 3. According to the sensing mechanism, wearable sensors are mainly sorted out to tactile/pressure sensors, strain sensors, electrophysiological sensors, electrochemical sensors and temperature sensors to measure various indicators of chronic diseases. The related techniques (such as materials, structures, and manufacturing) of these wearable sensors can be found in Section IV and Section V. Wearable pressure sensors (see more details in Subsection A of Section V) are used to detect blood pressure [26], [27], and to track breath and heart rate [28] as well as to analyze gait phase [29]–[31]. Human motion detection and daily activity monitoring can be carried out by wearable strain sensors (see more details in Subsection B of Section V) based on physical measurements [32]. Electrophysiological signals, such as ECG [33], EEG [34], EMG [35] and EOG [36] can be collected by electrophysiological sensors (see more details in Subsection C of Section V). Wearable electrochemical sensors (see more details in Subsection D of Section V) measure real-time bio-parameters such as blood glucose [37], pH, hydration [38] and lactate in contact with the skin [39] through body fluids, such as sweat, saliva, blood, urine, and tears. Other respiratory ingredients [40] and its humidity [14] can also be detected by wearable electrochemical sensors [41]. Wearable temperature
sensors (see more details in Subsection E of Section V) are attached to the skin to monitor the human body surface temperature to prevent dehydration and heat stroke [42]. This section will cover these five kinds of wearable sensors and bridge the gap between wearable sensors and applications in chronic disease care.

A. Blood Pressure and Heart Rate Tracking

Blood pressure (BP) and heart rate are vital signs in the cardiovascular system, which are influenced by cardiac output, total peripheral resistance and arterial stiffness and depended on the age, emotional state, activity, and relative health/disease states. Continuous and long-term BP monitoring is extremely important for the diagnosis of chronic cardiovascular diseases. For example, long-term hypertension is a risk factor for heart disease, stroke and kidney failure and often goes undetected because of infrequent monitoring and the less obvious symptoms. The two most significant parameters in BP are the systolic blood pressure (SBP) and diastolic blood pressure (DBP). Traditionally, these two parameters are most commonly measured via a sphygmomanometer or stethoscope, which historically occlude the blood flow of the patient by an inflatable cuff and used the height of a column of mercury to reflect the circulating pressure [25]. The most common automated measurement technique is based on the small oscillations in the pressure of the cuff to obtain the two parameters. Compared with the conventional sounds-heard strategies that are intermittent and obtrusive to cause discomfort, wearable sensors pave the way for the new clinical method of continuous BP monitoring by collecting and processing the BP pulse waveform [43], [16]. BP pulse waveform is induced by the heart muscle contracting and pumping blood from the chambers into the arteries and provides useful information (e.g., SBP, DBP, heart rate and aged/stiff blood vessel) on a possible cardiovascular disease through non-invasive wearable sensors [23], [31], as shown in Fig. 4(a). The two most common types of
Typically, a wrist pulse waveform contains three main waves: percussion wave (P-wave), tidal wave (T-wave), and diastolic wave (D-wave) \[ \text{Fig. 4(b)} \], where P-wave is the early systolic peak pressure, T-wave is the late systolic peak pressure and D-wave appears in the diastole region and is referred to as the diastolic pulse waveform [44], [45]. Because the healthy young people have low vascular resistance and good elasticity, the high and narrow P-wave shows a mountain-like shape. Clinically significant parameters can be extracted from these three main waves, such as the radial arterial augmentation index (AI) defined by T-wave/P-wave, the radial diastolic augmentation (DI) defined by D-wave/P-wave, the time delay ($\Delta T_{DVP}$) defined by the time interval between the P-wave and T-wave, the stiffness index (SI) defined by $H/\Delta T_{DVP}$ (where $H$ is the height of the human subject), and the heart rate that is the frequency of cardiac cycles. Among various types of sensors, electrophysical sensors (e.g., tactile/pressure sensors [46]–[50], strain sensors [45], [51], and electrophysiological sensors) and optical sensors [27] are the most promising candidates for BP pulse wave and heart rate monitoring [52]–[57]. The recent typical wearable sensors used in BP pulse waveform tracking with nano-based enhancement are summarized in Table I.

In the following, several typical examples of wearable sensors with nano-based enhancement for the applications in BP monitoring and BP pulse waveform tracking are presented. Luo et al. [25] developed a flexible piezoresistive sensor (FPS) based on carbon nanoparticles (CB). They also demonstrated an epidermal BP pulse and ECG combined sensor to extract real-time beat-to-beat BP data based on pulse transit time (PTT) method [Fig. 4(c)–(h)]. The PTT method calculates the BP based on the time interval between the R-peak of the ECG and a feature point of the pulse wave signal of the same cardiac cycle to provide the SBP and DBP at each heartbeat. They compared the average of the beat-to-beat SBP and DBP recorded by their device with the readings from OMRON that was a commercial cuff-based device. The average DBP based on the PTT method showed <4 mmHg difference with the readings provided by OMRON.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Sensor type</th>
<th>Pressure</th>
<th>Sensitivity</th>
<th>Stability (cycles)</th>
<th>Volunteer</th>
<th>Pulse type</th>
<th>Pulse rate (times/min)</th>
<th>AI</th>
<th>DI</th>
<th>$\Delta T_{DVP}$ (s)</th>
<th>SI (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[44]</td>
<td>Carbon nanotubes (CNTs)/Polydimethylsiloxane (PDMS)</td>
<td>0.101 kPa$^{-1}$</td>
<td>5x10$^3$</td>
<td>Male, 24 years old</td>
<td>Wrist</td>
<td>70</td>
<td>0.45</td>
<td>--</td>
<td>0.22</td>
<td>--</td>
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</tr>
<tr>
<td>[45]</td>
<td>Graphene/Silicon rubber (Dragon Skin)</td>
<td>142 (Gauge factor)</td>
<td>2x10$^3$</td>
<td>Male</td>
<td>Wrist</td>
<td>60 (rest)</td>
<td>--</td>
<td>--</td>
<td>0.31</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>[46]</td>
<td>Zinc oxide nanorods/PDMS</td>
<td>0.768 kPa$^{-1}$</td>
<td>--</td>
<td>Male</td>
<td>Wrist</td>
<td>70</td>
<td>0.6</td>
<td>0.25</td>
<td>0.31</td>
<td>--</td>
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</tr>
<tr>
<td>[23]</td>
<td>Graphene/PDMS</td>
<td>25.1 kPa$^{-1}$</td>
<td>3x10$^3$</td>
<td>Male</td>
<td>Wrist</td>
<td>70</td>
<td>--</td>
<td>--</td>
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<tr>
<td>[31]</td>
<td>Reduced graphene oxide (rGO)/Polyvinylidene fluoride</td>
<td>47.7 kPa$^{-1}$</td>
<td>5x10$^3$</td>
<td>Male</td>
<td>Wrist</td>
<td>72</td>
<td>0.472</td>
<td>0.264</td>
<td>0.196</td>
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</tr>
<tr>
<td>[47]</td>
<td>SWNT/tissue paper</td>
<td>2.2 kPa$^{-1}$</td>
<td>--</td>
<td>Male, 34 years old, 170 cm tall, 65 kg weight</td>
<td>Wrist</td>
<td>68</td>
<td>0.65</td>
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</tr>
<tr>
<td>[43]</td>
<td>CNTs/PDMS</td>
<td>9.55 kPa$^{-1}$</td>
<td>1.5x10$^3$</td>
<td>Male</td>
<td>Neck</td>
<td>64</td>
<td>--</td>
<td>--</td>
<td>0.35</td>
<td>--</td>
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</tr>
<tr>
<td>[51]</td>
<td>PbTiO$_3$-nanowires/Graphene/PDMS</td>
<td>9.4x10$^{-1}$ kPa$^{-1}$</td>
<td>--</td>
<td>Male, 29 years old, 175 cm tall, 72 kg weight</td>
<td>Wrist</td>
<td>70</td>
<td>--</td>
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</tr>
<tr>
<td>[52]</td>
<td>CNTs/Graphene/fabric</td>
<td>1000 (Gauge factor)</td>
<td>10$^4$</td>
<td>Male</td>
<td>Wrist</td>
<td>110</td>
<td>--</td>
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<tr>
<td>[53]</td>
<td>Graphene/PDMS</td>
<td>0.09 kPa$^{-1}$</td>
<td>--</td>
<td>Male</td>
<td>Wrist</td>
<td>78</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td>[54]</td>
<td>Graphene/PDMS</td>
<td>15.6 kPa$^{-1}$</td>
<td>10$^3$</td>
<td>24 years old, 170 cm tall, 55 kg weight, male</td>
<td>Wrist</td>
<td>80</td>
<td>--</td>
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<tr>
<td>[55]</td>
<td>Polyamine nanofibers/PDMS</td>
<td>2.0 kPa$^{-1}$</td>
<td>10$^4$</td>
<td>169 cm tall, 26-year-old female</td>
<td>Wrist</td>
<td>66</td>
<td>0.51</td>
<td>--</td>
<td>--</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>[48]</td>
<td>Gold nanowires/Tissue paper</td>
<td>1.14 kPa$^{-1}$</td>
<td>5x10$^4$</td>
<td>37-year-old male</td>
<td>Wrist</td>
<td>66 (rest) 88 (exercise)</td>
<td>0.7</td>
<td>--</td>
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</tr>
<tr>
<td>[52]</td>
<td>Silicon nanomembranes</td>
<td>0.005 Pa (limit)</td>
<td>10$^3$</td>
<td>A healthy female in her late twenties</td>
<td>Wrist</td>
<td>--</td>
<td>0.45</td>
<td>--</td>
<td>0.2</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>[57]</td>
<td>Silver nanoparticles/PDMS</td>
<td>0.3 kPa$^{-1}$</td>
<td>800</td>
<td>Male</td>
<td>Wrist</td>
<td>--</td>
<td>0.53</td>
<td>--</td>
<td>--</td>
<td>4.6</td>
<td>--</td>
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TABLE I
SUMMARY OF TYPICAL WEARABLE SENSORS FOR BLOOD PRESSURE PULSE WAVEFORM MONITORING
of the ECG and the AC peak of the SCG. Kim et al. [59] provided a wearable sensor to monitor BP with pulse arrival time (PAT) which was calculated by ECG and blood pulse wave. In their study, conformable and stretchable ECG dry electrodes and an accelerometer printed by silver nanoparticles (AgNPs) were assembled and attained clear ECG signals which were comparable in shape and strength with those from the conventional wet electrode. By utilizing their wearable sensor, the PAT was extracted from the time interval between the R-peak of the ECG signal and the starting point of the pulse wave. Finally, a fitting line which was obtained from the graph of PAT and reference BP was used to estimate BP reliably.

In addition to flexible piezoresistive sensor for pulse wave detection, the combination of flexible light-emitting diode (LED) and photodetector is another promising way for monitoring of BP. This method adopts monitoring of photoplethysmogram (PPG) and provides convenient and intuitive measurements for evaluating BP and heart rate. Xu et al. [60] developed an flexible and wearable near-infrared PPG sensor consisting of a low-power, high-sensitivity organic photodetector and a high-efficiency inorganic LED. Combining with ECG measurements, the nanostructured flexible PPG sensors were able to continuously monitor the variation of heart rate and precisely track the changes of BP under different postures of human subjects. The developed flexible PPG sensor showed more reliable performance than PPG sensors integrating
commercial available silicon-based photodetectors (e.g., Model VTD34SMH from Excelitas Technologies and Model OPT101 from Texas Instruments). Liu et al. [61] proposed a highly-compact multi-wavelength PPG (MWPPG) module and a depth-resolved MWPPG approach for continuous monitoring of BP and systemic vascular resistance (SVR). Compared to traditional noninvasive or continuous methods, the proposed depth-resolved MWPPG approach were capable of providing accurate measurements of SVR and BP. The developed MWPPG sensor can be further implemented in various wearable platform to comprehensively monitor cardiovascular health parameters including heart rate, blood oxygen saturation, SVR and BP.

### B. Human Body Temperature Measuring

Human body temperature is one of the most important health parameters for chronic disease care. There are many factors that affect individual body temperature, such as time of the day, the patients’ state of consciousness (e.g., waking, sleeping and sedated), activity, health, and emotion. Abnormal body temperature indicates that the patient’s health is seriously threatened by disease such as cardiovascular diseases and stroke [13]. A deviation of few degrees between body temperature and the average value of 37 °C may cause impairment of organs in the human body and even death [6]. Therefore, real-time uninterrupted monitoring of body temperature is extremely important for chronic disease care, such as cardiovascular health, pulmonological diagnostics, breast cancer, and other syndromes [6]. Traditional measuring method requires the medical thermometer to be inserted into the patient’s body (e.g., esophagus, rectum, mouth, external auditory meatus and tympanic membrane), causing discomfort and potential infection for patients [13]. Wearable sensors provide a new way to measure the human body temperature at various locations with a stable temperature measurement. Specific parts of the body must be carefully selected to mount the wearable sensors so that readings can truly reflect the core temperature of the human body even during the environmental temperature change. Currently, some wearable sensors monitor the human body temperature by mounting them at the sub-lingual, axillary, forehead, temporal artery, ear, armpit, chest, and abdomen [39].

Among various types of sensors, temperature sensors are the most promising candidates for continuous human body temperature measuring. Yang et al. [62] demonstrated the capability of their prototype temperature sensor as a wearable device and utilized it to measure the temperature of the human body [Fig. 5]. After calibrating the sensor, they attached the sensor to the back of a hand and measured the resistance of the sensor. From the measured resistance of 1345.8 Ω, the body temperature was estimated to be 35.6 °C according to the fitted linear function indicating that the sensor was sensitive enough to monitor human body temperature. Lou et al. [16] demonstrated the potential of the ultra-thin temperature sensor in biomedical applications by attaching the ultrathin e-skin sensor on the
forehead of an adult male to record body temperature. The sensor had a conformal and better contact with the skin, which was benefiting from the ultrathin PDMS substrate and shown that the conductivity of the sensor was increased when the sensor was attached on the forehead. Ho et al. [63] developed a flexible graphene-enabled sensor array that can map the distributions of the corresponding temperature, humidity, and pressure during the finger pressing event. Kim et al. [64] presented a sensor array with fully inkjet-printed flexible conducting electrode using AgNPs ink. When the finger was placed on the sensor array, it responded to both pressure and temperature. Vuorinen et al. presented fully printed temperature sensors based on Au nanoparticles on nanocelllose substrate [65] and graphene/PEDOT:PSS compound [66]. These sensors were fabricated on soft and thin polyurethane (PU) substrates enabling unobtrusive way to mount on the human skin.

C. Human Daily Activity Monitoring

People’s daily behavior mostly affects the individual state of health. Keeping track of everyday activity helps to improve the quality of life and provides valuable insights into wellness of human beings. For instance, human daily activity is an important feedback during stroke rehabilitation and provides quantitative data for precision medicine [67]. At present, one of the most widespread methods to realize daily health management for chronic disease care is to adopt wearable sensors [68] to measure common health parameters such as walking steps, heart rate, human joint motion and muscle movement/tremor, and to measure body posture during sleep to reflect the quality of sleep [69], [70]. Patients get the assessment of their health status based on the measurement data through the applications installed on mobile terminals via established communication from wearable sensors. Part of the measurement and analysis results are uploaded to the cloud server through the mobile network for storage, which establishes a wireless connection between the patient and the caregiver from different medical centers. Combined with a cloud server, doctors at different hospitals with specialized knowledge on various chronic diseases can analyze raw data to identify abnormalities, and timely access to patients to adjust treatment [71].

Among various types of sensors, electrophysical sensors (e.g., tactile/pressure sensors, strain sensors, and electrophysiological sensors) are the most promising candidates for human daily activity monitoring. Liao et al. [72] investigated the behaviors of the bending strain sensor using gold nanofilm for detecting the bending-stretching motion of a finger under the spraying condition [Fig. 6(a)]. The high signal-to-noise ratio (SNR) of the strain sensor was well-maintained to detect the bending angle of a finger even under a humid or wet condition without any other modifications. Zheng et al. [73] developed a wearable strain sensor based on CNTs-CB/PDMS composite that was assembled to detect the human joint motion (such as the motion of finger, wrist, elbow and knee). These sensors were fabricated on soft and thin polyurethane (PU) substrates enabling unobtrusive way to mount on the human skin.

![Image](https://via.placeholder.com/150)

Fig. 6. Flexible and stretchable wearable sensors for human daily activity monitoring. (a) Finger bending detections of the AuNPs-based strain sensor before and during sprayed with pure water by Liao et al. Reprinted with permission from [72]. Copyright 2017, American Chemical Society. (b) A wearable device based on nanocomposite for self-powered physiological monitoring of eye blinking. (c) Arm bending, and (d) speaking by Chen et al. Reprinted with permission from [70]. Copyright 2017, American Chemical Society.
acoustics, pulse, finger motion, and respiration. The integrated wearable monitoring system could collect and transmit the health data to a smartphone via Bluetooth communication. Moreover, they developed an application in a smartphone to share the health data of patients with caregivers by uploading the health information to the cloud server. Furthermore, a wireless neck posture corrector was developed to monitor neck flexion and gave a warning via the voice function of the smartphone. In addition, a wearable fall detector was designed and built to monitor the walking patterns and detect possible falls, both of which were vital in mobile health monitoring for the elderly. Zhou et al. [74] developed a polyaniline nanofibers (PVDF NFs) enabled the pressure sensor to detect subtle stresses, which was attached to the human face to monitor facial muscle movement. When the patient repeatedly bit the teeth, the pressure sensor instantaneously generated a synchronous current response because of the movement of the facial muscle. Additionally, the pressure sensor was attached to a human throat, showing a significant change in current when the patient sang a song.

D. Glucose and Drug Monitoring

Continuous capture and analysis of analyte (e.g., sodium ions (Na⁺) and potassium ions (K⁺), pH, urea, lactate and glucose) in body fluids (e.g., sweat, tears and saliva) offer a high clinical value for remote chronic disease care, which is a key advantage offered by wearable sensors. Among various types of sensors, electrochemical sensors are the most promising candidates for body fluids analysis.

Diabetes is one of the most common chronic diseases that occur due to an imbalance in the blood glucose levels of the body [20]. Optimum diabetes management needs continuous blood glucose monitoring to provide a trend of blood glucose level, which is more meaningful than an accurate data point for pre-diagnosis. Traditional finger puncture is an invasive method. However, high-frequency blood sampling monitoring imposes a burden on the patient’s physiology and psychology and raises the risk of infection, which is not suitable for long-term continuous blood glucose monitoring. Currently, many researchers provide us with a minimally invasive sensing method by using enzyme-based microneedle. For example, a research group invented a nano-ink tattoo that matched the sensor injected under the skin to achieve real-time blood glucose monitoring in the skin interstitial fluid [75]. However, this method cannot offer completely non-invasive monitoring. Further development, non-invasive wearable sensors have been proven to be convenient, real-time, and safe for the detection of glucose levels, through the analysis of body fluids. Glucose is found in the human sweat with the concentration range of 0.1–50 mg/dL [76]. There is currently a good correlation established between blood and sweat glucose levels [76]. Ban-dodkar et al. [18] presented a device to measure blood sugar levels without taking blood. The team printed the electrodes on a temporary tattoo and linked the sensor, as glucose was loaded with sodium ions and had a positive charge. The sensor measured the intensity of the charge under the skin and calculated the glucose content in the blood. The feasibility of this non-invasive blood glucose monitoring was demonstrated by a postprandial blood glucose test on seven non-diabetic subjects. Munje et al. [76] demonstrated a wearable and flexible electrochemical sensor for the combinatorial label-free detection of glucose in human sweat by using zinc oxide (ZnO) deposited...
on nonporous polyimide (PI) membrane. Chen et al. [77] fabricated an efficient flexible glucose sensor based on multi-walled carbon nanotube (MWCNT) coated carbonized silk fabric for the electrochemical detection of glucose successfully. In addition to blood glucose monitoring, the value of pH reflects the state of many clinical conditions, such as wound monitoring [78]. The information provided allows patients to know when it is necessary to rehydrate themselves. In addition, changes in pH of the skin take part in the development of chronic skin disorders such as dermatitis, ichthyosis and fungal infections. Zamora et al. [79] presented a nanostructured textile-based and highly sensitive pH sensor for pH detection by means of stainless steel mesh. Yoon et al. [80] fabricated a flexible and thin pH sensor using a two-electrode configuration, which was comprised of a polyaniline (PAN) nanopillary array working electrode and a silver/silver chloride (Ag/AgCl) reference electrode for wearable healthcare. More so, the electrolytes, such as Na+ and K+, are also key indicators of chronic disease care, which reveal the amount of sweat caused by exercise [81]. Gao et al. [12] presented a wearable sensor array by using ion-selective electrodes (ISEs), coupled with a polyvinyl butyral (PVB) coated reference electrode. The robust measurement of Na+ and K+ levels was enhanced through the poly (3,4-ethylenedioxythiophene)-poly (styrene sulfonate) (PEDOT:PSS) in the ISEs, and CNTs in the PVB reference electrodes. The developed sensor was packaged and worn on a human subject for real-time perspiration monitoring on the wrist and forehead simultaneously during stationary leg cycling, as shown in Fig. 7(a). Besides, wearable sensors can also be used for drug monitoring through body fluids analysis, which plays crucial roles in doping control and precision medicine. The conventional method for drug monitoring is blood analysis, which provides the most direct and accurate approach to track drug dosage. Unfortunately, it is an invasive and time-consuming technique with limited sample collection. Easy-to-access human sweat with the various analyte is an ideal candidate for point-of-care health monitoring, which help physicians optimize drug dosage and track patients’ health status to prescriptions. Tai et al. [82] presented a wearable sensor equipped with a printed carbon working electrode modified with CNTs/Nafion films for drug monitoring [Fig. 7(b)]. A methylxanthine drug, caffeine, was selected to demonstrate the functionalities of the wearable sensor, which showed that their work leveraged a wearable sensor toward non-invasive and continuous point-of-care drug monitoring. From existing advances, the development of wearable non-invasive electrochemical sensors would be extremely beneficial for managing chronic diseases, provide customized therapies, and reduce the cost burden on the patients [76]. Apart from the above applications in body fluids analysis, wearable electrochemical sensors are capable of analyzing the breath gas to detect and diagnose chronic respiratory diseases, as shown in Fig. 7(c).

E. Gait Analysis Based on Plantar Pressure

Gait analysis is the systematic study of human motion, which is used to assess and treat individuals with conditions affecting their ability to walk, such as structural disorders, foot illness, or early diagnosis chronic disease [83]. Besides, gait analysis is often employed to diagnose physical and mental, generative or degenerative disabilities and diseases, which are well characterized by chronic gradual changes in the body mostly hands and feet movements. Traditionally, there are many established methods using various sensors for gait analysis, such as kinematics by using video cameras, dynamic electromyography by using EMG sensors, and temporal/spatial pressure measurement by using pressure sensors. Pressure measurement systems are an additional and the most often employed way to measure gait by providing insights into pressure distribution, contact area, the center of force movement speed and symmetry between feet during human motion [5]. Those parameters are vital references for gait analysis in the detection of abnormalities (e.g., the type of foot: flat, plano valgus, and clubfoot), diagnosis and therapeutic evaluation of human motion system diseases (e.g., Parkinson’s disease, Creutzfeldt-Jakob disease, Huntington’s disease, and Alzheimer’s disease). These diseases are detectable when the inappropriate pressure distribution is presented in the measuring result [5]. For instance, the monitoring foot pressure of diabetic patients who lose the sensation of pain and temperature in their feet is transcendental to prevent complications such as ulcers, pathological neuropathy, infections, and even amputation. The absence of adequate sensation also changes the walking pattern unconsciously. Abnormal pressure distributions indicate a risk area of ulcer recurrence when the plantar pressure increases. Different methods for recording and assessing pressure are available, such as footprint method, force plate (a walkway longer in length to capture more foot strikes), pressure measurement mat, and in-shoe or insole pressure measurement systems (where sensors are placed inside the shoe or the sole). Force plate is the most widely used equipment for plantar pressure measurement, but it is generally used in a static situation that does not correspond with remote gait analysis [84]. The simplest pressure insole/in-shoe can overcome the disadvantage of force plate and other methods, because the in-shoe systems can fit the foot softly and allow the measurement under various conditions without causing inconvenience and discomfort to the wearer.

User-friendly wearable pressure sensors have been increasingly introduced in research and clinical practice in plantar pressure detection, which can be integrated insoles or shoes to extract data for analysis. These sensors make it easier and more straightforward to measure gait parameters and analyze relevant data for remote health monitoring, rehabilitation, and disorder pre-diagnosis. For example, Gerlach et al. [85] presented a low-cost and flexible plantar pressure monitoring system that was suitable for daily use to prevent pressure ulcerations [Fig. 8(a)]. The pressure sensor element was prepared by the MWCNT/PDMS composite. The flexible conductive interconnections were fully printed for the pressure-sensing elements to enable pressure distribution measurements. Finally, a printed insole was fabricated with six single MWCNT/PDMS-based pressure sensors to detect the abnormal walking patterns. Lou et al. [84] developed a flexible pressure sensor based on the multilayer graphene films integrated on polyester textile, which was adopted to construct a stable wireless plantar pressure in-shoe measurement system to monitor dynamic pressure distribution on foot in real-time. The developed pressure sensor showed the advantage of wide dynamic pressure-sensing range, good flexibility and comforta-
bility, which provided the high possibility for clinical gait analysis. Park et al. [29] developed a flexible capacitive pressure sensor based on the typical structure that PDMS as a dielectric layer was sandwiched between two MWCNT/PEDOT:PSS composite electrodes for gait analysis. Lee et al. [31] demonstrated a flexible ferroelectric rGO/PVDF-based pressure sensor with ultrahigh sensitivity and linear response over an extremely broad pressure-sensing range. The developed pressure sensor was fabricated with a multilayer interlocked micro-dome geometry, enabling to monitor various stimuli over extremely broad pressure-sensing range including weak gas flow, acoustic sound, wrist pulse pressure, respiration, and foot pressure on a single wearable sensor [Fig. 8(b)].

F. Brief Conclusion

Although some developed wearable sensors have been initially validated for chronic disease care, most of the developed sensors do not fully meet the diagnostic needs (see BP monitoring in Table ), nor do they enable true long-term wearable monitoring due to the lack of subsequent integration. In order to realize long-term remote chronic disease care, more efforts should be devoted to the development of integrated wearable system based on various wearable sensors. Wearable system combined with mobile terminals consists of wireless transmission and the establishment of unified cloud services, should achieve real-time health data transmission, analysis and feedback. In addition, wearable sensors should be broadened, especially in the chronic disease care. In the future most of the chronic diseases should be diagnosed or even cured at home with the development of the wearable system, especially the research of wearable sensor based on nanomaterials and nanotechnology. Flexible and stretchable wearable sensors will be increasingly and widely used in chronic disease care with the continuous deepening of related physics, chemistry and information basic research and technologies, as well as the continuous advance of new materials.

III. REQUIREMENTS OF WEARABLE SENSORS

To be applied in chronic disease care, wearable sensors must satisfy the requirements for flexibility and stretchability as well as other vital sensing characteristics. Because the quality of sensing data directly influences the diagnosis results, doctors pay more attention to the sensitivity, reliability and accuracy of wearable sensors. These characteristics comprehensively evaluate the feasibility of wearable sensors for chronic disease care. From the patient’s perspective, they interact physically with the wearable sensor, which means that the comfortability, durability and portability of the wearable sensor are the main considerations. In this section, this review exploits a comprehensive investigation onto requirements for wearable sensors from two different perspectives, as shown in Fig. 9. The typical examples of different platforms are briefly presented in this section.

A. Doctor Perspective for Feasibility

1) Pressure/Tactile Sensors: Wearable pressure/tactile sensors adopt transduction mechanisms which rely on the change in geometry to sense the pressure and contact force. The major geometry deformations of wearable pressure/tactile sensor are compression and bending. High sensitivity and fast response time, are major requirements of pressure/tactile sensor used for chronic disease care. In addition, to enable the same pressure/tactile sensor to be applied to different occasions, they should have a wide dynamic sensing range and linear sensing capability to constantly maintain their high sensitivity. For example, to
cover the full required pressure-sensing range for chronic disease care, pressure sensor with high sensitivity should perceive subtle pressure of a breathing and respiration (<1 kPa), medium pressure of blood pulse pressure and gentle touch (1–10 kPa), and large pressure of plantar foot pressure (>10 kPa) [31]. Apart from the requirements on sensor sensitivity, fast response time, and linear wide sensing range, high repeatability and the accurate corresponding relationship between pressure input and electrical output are always in demand. The latter require pressure sensors to have no loading-unloading hysteresis [86]. Sensor repeatability refers to the reproducibility of pressure response from multiple sensors, in cyclic loading and over long-term working. Since the pressure value are extracted from the initial calibration of the corresponding relationship between pressure input and electrical output, it is essential that the sensor maintains this relationship throughout its lifetime to achieve good measurement accuracy and reliability. It should be noted that, to make the sensor applied in real biomedical application, it should not only exhibit reproducibility, but also bending reliability [87]. The sensors are often applied on curved surfaces and pressed by soft human body in biomedical applications [88]. In this case, the normal pressure cannot be measured independently from the mechanical stress/bending [89]. A good bending reliability ensure the sensor to offer stable pressure readings under bending. The sensor transfer curve under bending will be different from that under flat condition. To mimic the real situation, where the flexible sensor is used under bending condition such as monitoring the arterial pulse or breath, bending reliability of the flexible sensor is a key issue [89]. One practical example has been reported to improve bending reliability (a measurement error below 6% under bending radius variations from -25 to +25 mm) by optimizing the density and thickness of the sensing composite [88]. Besides, for large-scale applications such as sensor networks and sensor arrays, variations in individual sensor characteristics should be minimized to reduce the computational load on signal processing [86], which meets the increasing requirement for device miniaturization and low power consumption [31].

2) Strain Sensors: As shown in Fig. 9(f), strain sensors can transduce the mechanical strain into electrical signals during deformations, such as stretching and releasing [90]. Wearable electronics that can be embedded on clothing or mounted on the human skin used for chronic disease care requires strain sensors to be able to deform and closely attach on arbitrary surfaces to realize accurate signal monitoring [91]. In other words, the strain sensors should possess excellent flexibility, superior stretchability, wide strain sensing range, low detection limit, fast response and recovery speeds in addition to being highly sensitive to strain (ε) [73]. Compared to pressure/tactile sensor, the stretchability of wearable strain sensor is more important. In terms of stretchability, to monitor large deformations associated with human joint motions, it requires the strain sensor to be stretchable from 55% to 100% [91]. To monitor subtle deformations in throat, chest, and face etc. induced by blood pulse, breathing, facial expression, speaking, swallowing and so on requires the detection limit of strain sensor to be as small as 0.1% [2]. Moreover, the skin-attached strain sensors should be stretchable in a similar level with human skin (avg. of ε ≈ 25.45 ± 5.07%) to form the intimate contact with human skin [92]. Additionally, the stability/reliability of the strain sensor is another important factor because strain sensing applications in chronic disease care typically require stable electrical output behavior under long-term cyclic strain [90]. This requirement of strain sensor is similar to pressure/tactile sensor. Furthermore, strain sensors are required to be optically transparent when integrated into a multi-component wearable system. Wearable strain sensors should not hinder the transmission of light, which is commonly used by display screens to convey information or by photovoltaic cells to harvest energy [93].

3) Electrophysiological Sensors: Electrophysiological sensors are sensing electrodes attached to the human skin to detect various electrophysiological signals. However, the human skin is a dynamically moving curved surface and exhibits roughness at the micro/nano scale [92]. Thus, the sensor with adhesives needs to be flexible to adhere to the skin [94]. Therefore, maintaining a good conformal contact between the sensor and skin is essential for obtaining precise electrophysiological signals [95]. To avoid slippage, delamination, and breakage, the electrophysiological sensors require sufficient adhesion force between the sensors and the skin surface. For instance, nanostructured electrodes with high-aspect-ratio pillars provided high adhesion force (~1.3 Ncm⁻²) even after 30 times peeling off [2]. In fact, standard EEG sensing electrodes are attached to the scalp with conductive paste, while hair being an obstacle to noiseless measurements. Commercial ECG sensing electrodes often require a gel film to obtain good adhesion. However, gel dries over time and dramatically reduces signal quality [96]. To address these limitations, several requirements for sensor characteristics (e.g., stretchability, conductivity and hydrophobicity) of soft and skin-compatible sensing electrodes must be satisfied. High stretchability (100%) and good conductivity (≥100 Ωcm) are beneficial to improving electrophysiological signal recording quality [2]. The water-repellent, self-cleaning electrodes (contact angle of ~151° for deionized water [2]) can be used underwater [97]. Sensing electrodes with good conductivity, good stretchability and reusable adhesive force in a dry form factor are essential requirements for continuously long-term electrophysiological recording in chronic disease care.

4) Electrochemical Sensors: Wearable electrochemical sensors in chronic disease care are often used for body fluid analysis and breath gas analysis through chemical-to-electric sensing mechanism [98]. These sensors require good stretchability of the electrodes (stretchability of 25–100%), suitable sensing range of analyte (for instance, glucose levels of 70–100 mg/dL for healthy person, 80–130 mg/dL for diabetic patient and 0.1–50 mg/dL in human sweat [76]), good selectivity (no interference among the analytes), good reproducibility (relative standard deviation (RSD): 1–5%), fast response [78] and high sensitivity [2]. In addition, wearable electrochemical sensors should possess enhanced multiplexed functionality [99], reliability, and ease-of-use through non-invasive monitoring of body fluids [76]. Furthermore, wearable electrochemical sensors are preferred to be optically transparent with the same reason of strain sensors [95].

5) Temperature Sensors: The skin temperature monitored by wearable temperature sensors can be an indicator of a
chronic condition in the human body. On account of the very slight change in the skin temperature even in the case of illness [94], the temperature sensors are required to have a high sensitivity and accurately respond to small changes. The accuracy requirement is down to ±0.1 °C in the temperature range of 37–39 °C, while for below 37 °C and above 39 °C is ±0.2 °C [2]. In addition to monitoring in real time with high precision, wearable temperature sensors are required to have good flexibility, good repeatability, fast response, wide sensing range (25–50 °C [2]) and long-time stability against ambient influences [6].

B. Patient Perspective for Usability

In contrast to other electronic devices, wearable sensor as a human-interface used in chronic disease care must: 1) be directly attached to the human body and allow convenient mounting/dismounting, 2) guarantee safe and reliable electrical operation, 3) be with unobtrusiveness and lightweight to avoid affecting the activities of the patients, and 4) be with comfortability and durability to minimize frequency of replacement for a long-term monitoring without risking the patients’ health. The key to satisfying all of these requirements is to develop an optimized device configuration combined with novel sensing structures, mechanisms and materials for excellent electrical and mechanical characteristics and thus to enable the widespread application of flexible and stretchable wearable sensors in chronic disease care [100].

In terms of structures, conventional wearable sensors (such as EEG sensor) are generally uncomfortable and cumbersome [96]. Patients want to maintain a good appearance, avoid publicizing their illnesses, and behave normally during wearing, which means that these existing wearable sensors are difficult to use for chronic disease care. Therefore, wearable sensors should enhance patient privacy and social activities through a novel designed structure, which enable inconspicuous physiological signals recording [96]. In terms of sensing mechanisms, the extraction of biomedical signals is changing from an invasive method (such as EMG using the inserting the sensing needles to detect the electrical potential) towards non-invasive method (such as surface EMG using the surface electrodes for electrophysiological sensors) that can avoid the bleeding with pain [101]. In terms of materials, to meet the requirements of long-term chronic disease care, the wearable sensors are required to be flexible, biocompatible and...
light-weight without provoking irritation of the skin. For example, in long-term EEG/ECG signals recording system, the gel-free sensing electrode is a critical requirement. The skin needs to be prepared by light abrasion, and in order to reduce the contact impedence wearable sensors often require a conductive gel or paste to be applied to the electrode-skin interface [102]. Such procedures are time-consuming and unsuitable for long-term recording because the signal quality is attenuated as the gel or paste dries out over time. In addition, the gel-based sensing electrode may cause the redness and inflammation of the skin, and lead to discomfort for the patients because they stick to the hair and are difficult to remove [96]. After removing the conducting gel film using novel nanomaterials (such as AgNWs and CNTs), wearable dry sensing electrodes that can avoid the discomfort of the patient in regular wearing has attracted more and more attention [103].

C. Typical Platforms on Human Body

Commercially available wearable sensors for healthcare still exist in the form of rigid electrodes, circuits and chips that are mounted on bands or straps to be worn on the wrist, chest, etc. [7]. Although they are capable of daily activity tracking, heart rate recording etc., the data quality is still far from medical [102]. The combination of flexible and stretchable electronics and nanotechnology as well as sensing technology opens new platforms for wearable sensors on the human body, such as patch, mask, earphone, tattoo, insole, textile etc. These sensors exist in the form of rigid electrodes, circuits and chips that are mounted on bands or straps to be worn on the wrist, chest, etc. Although they are capable of daily activity tracking, heart rate recording etc., the data quality is still far from medical [102]. The combination of flexible and stretchable electronics and nanotechnology as well as sensing technology opens new platforms for wearable sensors on the human body, such as patch, mask, earphone, tattoo, insole, textile etc. These sensors can fit tightly into the human body surface and accurately reflect the state of health for a long-term monitoring.

1) Patch: Wearable sensors are always directly attached to the skin during a long-time attachment in the form of a patch. Fig. 9(a) displays a patch on the chest of the human body during shower [97]. Yamamoto et al. [42] developed a wearable ECG sensor patch that was placed on an arm for 30 hours, demonstrating that the material used for the sensor does not attack skin in 30 hours. Although still in its infancy to implement the practical healthcare patch, the fundamental properties reported in their research are a step in that direction.

2) Mask: Wearable sensors can be integrated into the mask to enable facial skin and muscle movement monitoring and breath gas analysis. Yang et al. [104] developed a wearable facial mask to monitor the pain intensity of a patient by utilizing surface electromyogram (sEMG) sensors. The facial mask was fabricated by a flexible and stretchable material (PDMS) and embedded with sEMG sensors that were integrated on the inner side of the mask. The facial mask was seamlessly attached to the facial skin to achieve reliable sEMG measurement. The facial mask was easy-to-applied and largely saved the valuable time for the caregivers.

3) Earbud: In order to achieve the goal of unconscious and unobtrusive EEG recording, many researchers proposed in-the-ear EEG recording as a novel inconspicuous EEG recording method. Lee et al. [97] in 2015 fabricated CNT/PDMS-based canal-type ear electrodes for EEG recording. These ear electrodes were easier to position and wear, even without conductive gel/paste, as shown in Fig. 9(a). Besides, wearing with these sensing electrodes that are relatively against electromagnetic interference was more comfortable for patients. Furthermore, Lee et al. [105] in 2018 reported a customized earphone that can monitor EEG signals in real-time via a wireless module without losing original listening function. In addition, the SNR of the in-the-ear recording can be comparable to the on-scalp recording, since the distance between the ear and the auditory cortex of the brainstem is short [96].

4) Tattoo: Hair-thin and skin-soft epidermal electronics or E-tattoo are recently developed wearable electronics [Fig. 9(c)–(e)], which can be intimately attached to the human skin for long-term, high-fidelity biometric sensing [11]. In addition to lightweight and soft, seamless sensor-to-skin integration also is a great advantage of E-tattoo. Due to the roughness of the skin in the micro/nano scale, theoretical analysis has clearly shown that only ultra-thin and ultra-soft E-tattoo can fully conform to natural skin morphology without extra adhesives [102]. Such conformability enlarges the contact area between the sensing electrode/materials and skin, and thus lowers the contact impedance and the interface loss, which directly leads to a higher quality in recorded physiological signals and less susceptibility to motion [102]. Thinning a film to a few micrometers or nanometers scale should achieve an E-tattoo capable of covering the skin asperity conformally, resulting in a good comfort while wearing [42].

5) Insole: Pressure-sensitive insole can be used for the gait-parameter analysis in Section 4. In addition, the insole is the simplest form of the pressure sensor, because the in-shoe systems can fit the foot softly and allow the measurement under various conditions without causing inconvenience and discomfort to the wearer. However, there are many problems to be solved before applying insole pressure sensors for chronic disease care, such as long-term stability, mechanical durability, nonlinearity and hysteresis [29]. Fig. 9(i) shows a smart insole integrated into a shoe to monitor the foot pressure distribution during the patient’s walking.

6) Textile: The textile material is made of flexible fibers, which has the characteristics of the porous structure, high surface area, lightweight, good elasticity, high strength and good tear resistance [106]. Luo et al. [86] developed a textile-based sensor, which can be easily attached to various substrates, such as a woundplast, as shown in Fig. 9(h). By using CBs as electrical micro-contacts on the surface of the fiber and PVDF as a mechanical interconnection between the fibers, the response fluctuation caused by the inelastic deformation of the textile can be reduced.

IV. NANO-BASED ENHANCEMENT FOR FLEXIBILITY AND STRETCHABILITY

Wearable sensors are gong through a process of changing towards more flexible and stretchable to satisfy the requirements for chronic disease care. These complex integrated devices are typically composed of: 1) flexible/stretchable substrates, 2) conducting electrodes/interconnections, 3) flexible/stretchable sensitive materials, and 4) encapsulation. To achieve mechanical flexibility and stretchability of wearable sensors, two approaches, as shown in Fig. 10, have been employed wildly: flexible/stretchable structures (FSS) and flexible/stretchable materials (FSM). The former approach exploited nanomaterials to achieve large-area and scalable manufacturing procedures, while the latter case has advantages of extensive application abilities with facile layouts and fabrica-
tion strategies [105]. The summary of typical wearable sensors among all categorizations and their applications in chronic disease care are shown in Table A.

### A. Flexible/Stretchable Materials

1) **Sensitive and Conductive Materials**: Sensitive materials have one or more properties that can be significantly changed in a controlled fashion by external stimuli. On the contrary, conducting electrodes or interconnections are supposed to be stable in high conductivity during bending or stretching process of wearable sensors. With the advances of nanoscience and nanotechnology, wearable sensors commonly use nanomaterials as sensitive materials or conductive electrodes to achieve flexibility and stretchability. Nanomaterials, also called nanostructured materials, can be synthesized into different dimensions ranging from zero-dimension (0D) to one-dimension (1D) and two-dimension (2D). Most of the nanomaterials are printed onto/dispersed in elastomeric matrices, as shown in Fig. 10.

0D nanomaterials: Nanoscale Nanoparticles (NPs), such as gold nanoparticles (AuNPs) [107], silver nanoparticles (AgNPs), carbon black (CB) [108], [109]. 0D nanomaterials have unique properties due to quantum confinement and large surface area [110].

1D nanomaterials: (1) Nanofibers (NFs), such as carbon nanofibers (CNFs), polynylidene fluoride nanofibers (PVDF NFs) [111], [112], polyaniline nanofibers (PANI NFs) [113]. (2) Nanotubes (NTs), such as carbon nanotubes (CNTs) [114], [115], multi-walled carbon nanotube (MWCNT), single-walled carbon nanotube (SWCNT). (3) Nanowires (NWs), such as gold nanowires (AuNWs) [116]–[119], copper nanowires (CuNWs) [120], [121], silver nanowires (AgNWs) [122], [123]. (3) Nanorods (NRs). The carrier transport of 1D nanomaterials is more efficient compared to transport properties in 0D nanomaterials [110].

2D nanomaterials: graphene, [124], graphene oxide (GO), reduced graphene oxide (rGO), and graphite nanoplates (GNPs) [125]. etc. 2D nanomaterials show enhanced charge transport characteristics in planar wearable sensor structures [110].

The most convenient way to obtain high ductility with nano-based enhancement is to embed conductive nanomaterials into polymers to create polymer-conductive nanocomposites. These elastomeric nanocomposites provide benefits, such as enhancement of mechanically conformal contacts at interfaces between the skin and electrodes, leading to the allowance of recording high quality of electrophysiological signals [105]. Since nanoscale dimensions reduce the stiffness of materials, this helps mitigate the risk of mechanical failure during bending/stretching cycles [110]. Fig. 10(d) shows the CuNWs-based wearable strain sensor with a maximum gauge factor (GF) of 54.38 from 0 to 100% extension [120]. A GNP-based wearable strain sensor has a gauge factor of 0.9 at the strain variation of up to 30%, which is shown in Fig. 10(h) (k) [125]. The other way is to deposit nanomaterials on the surface of the flexible/stretchable substrate to form a conductive network. However, in order to achieve a high conductivity for excellent sensing detection, high concentrations of the conductive nanomaterials are required, leading to extremely low light transmittance and mechanical compliance of the polymer matrices [95].

2) **Flexible and Stretchable Substrate Materials**: The flexible/stretchable substrate is a key component of the wearable sensor. It is not only the support of sensitive materials but also the main flexible/stretchable part of the entire sensor. Therefore, portable, flexible, malleable, anti-corrosion insulation, surface adhesion ability on the skin, durability and other properties are all key indicators to evaluate flexible substrate. At present, various materials have been used as flexible/stretchable substrate materials, such as polylithiolsiloxane (PDMS) [126]–[128], silicone rubber (SR) (e.g., Ecoflex, Smooth-On, Inc. and Dragon Skin, Smooth-On, Inc.), polyimide (PI) [129], [130], polyethylene terephthalate (PET) [131], hydrogel, photosensitive polymer (SU-8) [132], PU

### Table II

**Summary of Typical Wearable Sensors with Different Implementation Methods**

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</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>FSM</td>
<td>CNTs/PDMS</td>
<td>–</td>
<td>Yes/Yes</td>
<td>Coating</td>
<td>Chest</td>
<td>Monitoring of the cardiovascular system</td>
<td>[33]</td>
</tr>
<tr>
<td>EEG</td>
<td>FSM</td>
<td>CNTs/TPU</td>
<td>38 hours</td>
<td>Yes/Yes</td>
<td>–</td>
<td>Forehead, earlobe</td>
<td>Epilepsy and stroke</td>
<td>[34]</td>
</tr>
<tr>
<td>EMG</td>
<td>FFS</td>
<td>Au</td>
<td>100 (reuse)</td>
<td>Yes/Yes</td>
<td>Photoetching</td>
<td>Submental</td>
<td>Head and neck cancer treatment</td>
<td>[35]</td>
</tr>
<tr>
<td>EOG</td>
<td>FFS</td>
<td>Au</td>
<td>10 (reuse)</td>
<td>Yes/Yes</td>
<td>Photoetching</td>
<td>Face</td>
<td>Ophthalmological diagnosis and recording eye movements</td>
<td>[36]</td>
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<tr>
<td>Pressure</td>
<td>FSM</td>
<td>AgNWs/PDMS</td>
<td>103</td>
<td>Yes/Yes</td>
<td>Printing</td>
<td>Chest</td>
<td>Heart rate collection</td>
<td>[28]</td>
</tr>
<tr>
<td>Strain</td>
<td>FSM</td>
<td>Graphene/PDMS</td>
<td>102</td>
<td>Yes/Yes</td>
<td>–</td>
<td>Neck, throat, wrist, forehead</td>
<td>Assist voicing, prevention of drowsy driving, heart rate collection and rehabilitation</td>
<td>[32]</td>
</tr>
<tr>
<td>Temperature</td>
<td>FSM</td>
<td>CNTs/PDMS</td>
<td>100 (reuse)</td>
<td>Yes/No</td>
<td>Printing</td>
<td>Arm/chest</td>
<td>Monitoring temperature</td>
<td>[66]</td>
</tr>
<tr>
<td>Glucose</td>
<td>FSM</td>
<td>AuNPs/PEDOT-PSS</td>
<td>5</td>
<td>Yes/Yes</td>
<td>Printing</td>
<td>Arm/chest</td>
<td>Monitoring temperature</td>
<td>[66]</td>
</tr>
<tr>
<td>Hydration</td>
<td>FSM</td>
<td>AgNWs/PDMS</td>
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<td>Yes/Yes</td>
<td>Coating</td>
<td>Wrist</td>
<td>Skin diseases diagnosis</td>
<td>[38]</td>
</tr>
<tr>
<td>Volatile organic compound (VOC)</td>
<td>FSM</td>
<td>rGO/PET</td>
<td>102</td>
<td>Yes/No</td>
<td>Coating</td>
<td>Wrist, chest</td>
<td>Diabetic and nephritic diagnosis</td>
<td>[41]</td>
</tr>
<tr>
<td>Humidity</td>
<td>FSM</td>
<td>CNTs/plastic foil</td>
<td>100</td>
<td>Yes/No</td>
<td>Photoetching</td>
<td>Skin</td>
<td>Sweat monitoring</td>
<td>[14]</td>
</tr>
</tbody>
</table>
[125], textile, fabric etc. Among these materials, hydrogels are good candidates for adhesive sensing electrodes, not only because of their high optical transparency and biocompatibility but also because of their good ionic conductivity which is one of the most widely investigated stretchable substrates. However, there are several limitations that hinder the further application of hydrogels. The adhesion force of hydrogels is not enough to maintain long-term conformal contact between the wearable sensors and the skin. Moreover, the quality of sensing data and mechanical properties of sensors decrease significantly over time goes by as the water in the hydrogels evaporates. Hence, most hydrogels cannot be applied to the dynamically moving parts of the human body for long-term chronic disease care, such as the elbow, fingers, and knee [95]. Numerous significant efforts have been devoted to finding other adhesives instead of hydrogels, such as SR, PU, and PDMS. Among these polymers, SR and PU are aggressive adhesives that are unsuitable for chronic disease care, because polymer residues are left on the skin following detachment and cause skin trauma, such as ripping, irritation and allergic reactions [95]. In contrast, PDMS can minimize the skin trauma and polymer residues. It possesses not only high stretchability and durability but also thermal stability, good biocompatibility, chemical inertness. The adhesion force of PDMS can be easily enhanced by mixing tackifier or additives into the formulation, such as poly(ethyleneimine) ethoxylated (PEIE) [95].

3) Encapsulation Materials: Encapsulants are used to package a wearable sensor to protect the sensor from undesirable environmental effects. Common packaging materials are epoxy resin, PDMS, PI, acrylic resin. The traditional packaging method is to encapsulate the substrate with a low permeability epoxy, but this method cannot be applied to flexible electronics because the encapsulated flexible electronics cannot ensure their deformability. By contrast, PDMS can satisfy the deformation requirements of flexible electronics, which is one of the most widely investigated stretchable substrate and packaging materials. Additionally, transparency and cost-effective fabrication process could also be advantageous for PDMS [133].

B. Flexible/Stretchable Structures

In the case of large and complex deformations (e.g., rotation,
Most conventional electronic devices are rigid, which means it will be broken easily during the large deformation of the human body. Besides, conventional electronics fabrication process, which needs high equipment investment, complex steps with chemical reaction, also limits its application in the field of wearable devices. Recently, photolithography/photoetching has been adopted to fabricate flexible and stretchable sensor. Based on photolithography/photoetching technology, most developed flexible and stretchable sensor showed attractive performance [35], [36]. Since the fabrication process includes metal evaporation and post processing, the implementation of flexible and stretchable sensor is sophisticated to some extend [14]. The new wearable sensors integrated on the human skin push a process of changing towards printed electronics (PE) [153]. Printing technology, as an electronic manufacturing technology, complements traditional micromachining technology. PE uses solution-based manufacturing processes, such as ink-jet printing [154], screen printing [155], gravure printing, roll-to-roll printing [158], aerosol printing [17], direct printing [123] and electrohydrodynamic printing (EHD printing) [159], [65]. Compared with traditional top-down lithography technology, printing technology has the advantages of bending and stretching, good fabrication on flexible/stretchable substrates, simple processing equipment, cost-effectively manufacturing process (as shown in Fig. 11). Because of this, the printing technology based on nano- and microsized materials has developed rapidly in recent years. This new type of precision assembly patterning technology can process micro and nanoscale pattern of nano-materials with the method of additive manufacturing. However, there are limitations of printing technology. For example, graphene, as one of the most popular choice of functional materials to realize flexible sensors, can be patterned through ink-jet printing. Compared to photolithography/photoetching, the resolution of graphene pattern is relatively low [160]. Additionally, a thermal annealing is necessary to increase the electrical conductivity of pattern [161]. Apart from printing technology, graphene can also be grown by chemical vapor deposition (CVD), but the mechanical properties of such graphene-based sensor are weaker than those required for flexible sensor [63], [162]. Graphene can be transferred from a growth substrate onto a target substrate by polymer-assisted transfer printing, but cracks may form during this process [102]. The
emerging technologies of Laser Scribed Graphene [163] and Laser Induced Graphene [164] show promise for graphene-based wearable sensor, which are also simple and cost-effective. These techniques enable graphene to be doped in patterns of arbitrary shape without physical contact between graphene and the tool, which only require a low-power visible laser system [165]. Additionally, these techniques allow transfer-free graphene to be patterned directly on flexible substrates or uneven substrates [166]. An attractive feature of these single step fabrication techniques is obviating of the need for time-consuming and labor-intensive photolithography or phototetching [165]. By using these emerging technologies, wafer-scale graphene patterns can be obtained in ~25 minutes [166]. Despite all these efforts, to realize a large-scale and cost-effective graphene patterning method with high feature resolution and process simplicity, many efforts still should be devoted to further exploring of these methods.

D. Brief Conclusion

At present, there are several commonly used Nano-based enhancement methods for wearable sensing electronic devices: 1) deposit nanomaterial on the surface of the flexible/stretchable substrate to form flexible/stretchable conductive nanonetwork; 2) nanomaterial embedded into the flexible/stretchable substrate to form nanonetwork or modify/enhance material properties (e.g., the piezoresistive/piezoelectric/dielectric/thermoelectric properties); 3) the micro- or nanostructured substrate to obtain high sensitivity. In addition to these nano-based enhancement approaches, wearable sensors need to explore new methods to improve sensor performance to satisfy the requirements for flexibility and stretchability. Regardless of the progress described in Section A, many challenges still lie ahead before the implementation of wearable sensors in practical applications. For example, wearable sensors are often affected by the external noise signals generated by the human body. To weaken the disturbance from these external noises, cost-effective packaging and manufacturing methods should be further investigated.

V. State of the Art

Numerous wearable sensors that can be applied to chronic disease care using different nano-based enhancement methods have been reported. This section summarizes the recent progress in wearable electrophysical sensors (tactile sensors, pressure sensors, strain sensors, electrophysiological sensors, and temperature sensors), wearable electrochemical sensors (for body fluids analysis and breath gas analysis) and wearable multifunctional sensors.

A. Tactile/Pressure Sensors

Wearable tactile sensors and pressure sensors have the same transduction mechanisms including piezoresistive [167]–[171] capacitive [172]–[174], piezoelectric [175], and triboelectric [176], which are crucial building blocks for potential applications in real-time health monitoring, artificial electronic skins, and human-machine interfaces [177]. Most tactile sensors are in the form of arrays and have a lower range of perception. Wearable pressure sensors that are used for healthcare should be highly compliant to accommodate the skin deformations and highly sensitive to capture lower pressure associated with bio-signals such as BP pulse wave and respiration rate. The summary of recent typical wearable tactile/pressure sensors with key performance indicators is shown in Table 1.

1) Piezoresistive:

Wearable piezoresistive tactile/pressure sensors are made of a material with a piezoresistive effect that is a physical process. When the material is mechanically deformed, its own resistance value changes accordingly, such as material resistance, tunneling resistance, and contact resistance. The piezoresistive sensors display various advantages, such as high sensitivity, fast response, simple fabrication process, low energy consumption and so on [169]. Over the past few years, abundant advanced wearable sensors have been proposed, fabricated and applied with nano-based enhancement.

a) Material resistance and tunneling resistance: Plentiful conductive nanomaterials have been embedded into the flexible and stretchable substrate to obtain changeable material resistance and tunneling resistance. For instance, Jung et al. [178] developed a flexible tactile sensor based on pressure-sensitive conductive rubber (CNT/PDMS nanocomposites), which was used to identify multi-dimensional force information with a measurement range (128 Pa–100 kPa). The developed sensor could detect down to 128 Pa in normal pressure and 0.08 N in shear force, respectively. Kim et al. [24] presented a wearable piezoresistive pressure sensor with high sensitivity and a simple architecture based on highly flexible and stable nanocomposite conductors. The nanocomposite was made by embedding a vertically aligned carbon nanotube (VACNT) forest into a PDMS matrix with irregular surface morphology. After assembling, their pressure sensor showed a considerable sensitivity of ~0.3 kPa−1 up to 0.7 kPa−1, a wide detectable pressure range of up to 5 kPa before saturation, a relatively fast response time of ~162 ms, and good reproducibility over 5000 loading-unloading cycles. The developed wearable sensor was suitable for detecting human motions ranging from subtle blood pulses to dynamic joint movements.

b) Contact Resistance: Alternative attractive approach to realize piezoresistive sensors with high sensitivity is based on the change of contact resistance between conducting materials during mechanical deformation [74]. Currently, various rational micro/nano structural designs, such as interlocked micro-convex, pyramid, and fingerprint structures, of wearable pressure sensors have been extensively explored to achieve high sensitivity and a broad range of usable pressures [24].

2) Capacitive:

Wearable capacitive sensors are mainly consisting of two electrodes and the dielectric composition or structured air gap in the middle of the two electrodes. The main principle is that when the sensor changes in geometry by the external force, the capacitance value will produce the corresponding variation. Compared to the piezoresistive sensor, such capacitive sensor has a high-frequency dynamic response. Most wearable capacitive pressure sensors adopted nano-based enhancement method that uses nanomaterials as conductive electrodes or nanomaterials filled dielectric sensitive composites. For example, based on graphene electrodes and a sandwich-like structure shown in Fig. 12(f), a wearable pressure sensor exhibited many merits including a high response sensitivity (0.33 kPa−1) in a low-pressure regime (<1 kPa), an ultralow detection limit as 3.3 Pa, excellent working stability after more than 1000
cycles, synchronous monitoring for human pulses (~1 Hz) and clicks [172]. Chhetry et al. [174] fabricated a flexible capacitive pressure sensor with high sensitivity by coating a microporous elastomeric dielectric prepared by coating PDMS onto conductive fibers. Conductive fibers were prepared by depositing conductive polymer obtained by embedding AgNPs into poly(styrene-block-butadiene-styrene) (SBS) polymer on the surface of Twaron fibers. To imitate a capacitive sensor, two microporous PDMS-coated fibers as two electrodes were cross-stacking to each other, which responded to external pressure by increasing the contact area and decreasing the distance between the conductive fibers. The micro-pores of pressure sensor could be integrated into clothes or garments through sewing or weaving for further application in healthcare.

3) Piezoelectric:

Wearable piezoelectric sensors use functional materials with piezoelectric effects, which are widely applied in pressure sensors for the detection of dynamic signals. However, piezoelectric effects require sensors to be loaded with the dynamic stress to drive the transient flow of electrons that induce the piezopotential arisen. Therefore, it is a challenge for piezoelectric-induced pressure sensors to measure static signals. Many nano-based enhancement methods were developed in recent years, such as piezoelectric nanocomposites, nano-material-based stretchable electrodes. Seminara et al. [179]
fabricated dielectric polymer tactile sensors using PVDF flexible sheets and AgNPs electrodes, as shown in Fig. 12(e). AgNPs contacts were patterned on both sides of PVDF films by means of inkjet printing. Chen et al. [51] presented a wearable pressure sensor with NWs/graphene heterostructures, which was capable of measuring static pressure. Compared with the conventional piezoelectric NWs or graphene pressure sensors, their wearable pressure sensor was advanced with a high sensitivity of up to 9.4×10^{-3} kPa^{-1} and a fast response time down to 5–7 ms.

4) Triboelectric:

Wearable triboelectric sensors utilize triboelectric effect to sense the pressure and the contact force. As a newly developed energy-harvesting technology, the triboelectric nanogenerator (TENG) that can convert ubiquitous mechanical energies into electric power with a coupled effect of contact-electrification and electrostatic induction are often used for wearable triboelectric sensors. Ouyang et al. [180] proposed a flexible triboelectric ultrasensitive pulse sensor with excellent output performance (1.52 V), high peak SNR (45 dB), long-term performance (107 cycles). Zhao et al. [181] developed a self-powered force sensor, which were able to provide a gauge factor of 1.44 V·N^{-1} within the range of 0.15–25 N and a long stability over 60,000 cycles. They embedded barium titanate nanoparticles (BTO NPs) into the nanofiber film to enhance sensitivity for pressure sensing. In their study, the test result showed 2.4 times enhancement of sensitivity because of the synergy of piezoelectric and triboelectric effects. Lin et al. [182] made a triboelectric based pressure sensor with a linear pressure sensitivity 0.068 VkPa^{-1} in the high pressure range (100 kPa–700 kPa). The developed sensor allowed to light up several hundred LEDs instantaneously because of the integrated TENG with the maximum power density reaching 0.9 W/m².

B. Strain Sensors

Wearable strain sensors adopt the similar transduction mechanisms as the tactile/pressure sensors discussed above including piezoresistive [183]–[189] capacitive [190]–[193], piezoelectric [194], [195], and triboelectric [196], [197]. Gauge factor (GF) (GF = (∆R/R)/ε, where ∆R/R is the relative change in resistance and ε is the applied strain) is usually quantified to
evaluate the sensitivity performance of wearable resistive strain sensors [91]. Traditional strain sensors usually adopted rigid metallic materials, such as metal foils and inorganic silicon, which have a limited strain range (<5%) and a relatively small gauge factor (GF ≈ 2) [185]. There is a need for sensors that can bear high strains for various applications [198]. Furthermore, advanced wearable strain sensors are developed for the monitoring of human motion, such as a wide strain range (e.g., to detect large deformations associated with human joint motions) and high sensitivity (e.g., to monitor subtle deformations induced by blood pulse, breathing, facial expression, and so on). It has been considered a more efficient approach for wearable strain sensors that utilizing nanomaterials deposited on/embedded in stretchable polymer substrates to address these issues. The high stretchability of 500% [50], GF>1800 [194], and low sensing range down to 0.007% [91] have been demonstrated by a combination of innovation in nanomaterials, fabrication technology, and mechanism optimization [185]. The summary of recent typical nano-enhanced wearable strain sensors with key performance indicators is shown in Table 4.

Most of the nano-based piezoresistive strain sensors consist of a network of 1D/2D nanomaterials deposited on the surface of a stretchable substrate or embedded inside a polymer going to be a sensitive nanocomposite. Conductive pathways are established by the overlapping nanomaterials, which tend to slide on the surface or inside the substrate under strain resulting in the change of conductivity. For example, a percolation network based on TiC2T, MXene/CNT composites was designed and fabricated into versatile wearable strain sensors [185]. The developed strain sensor showed an ultralow detection limit of 0.1% strain, high stretchability (≈130%), high sensitivity (GF ≈ 772.6), tunable sensing range (30% to 130% strain), and excellent reliability and stability (>5000 cycles) [185]. Wang et al. [91] reported a strain sensor based on network cracks formed in multilayer CNTs films/PDMS composites. Due to the formed network cracked easily, the developed strain sensor achieved high GF (maximum value of 87) and a wide sensing range (≈100%), an ultralow detection limit of 0.007%, and an excellent stability (1500 cycles). These advanced characteristics enable the sensor to be suitable for both subtle and large strain detection, such as artery pulses, music vibration and large-scale motions of joint bending.

Nano-based stretchable conductors are good choices as the electrodes for capacitive strain sensors to achieve a higher stretchability. For instance, Kim et al. [93] developed a capacitive strain sensor with an enhanced sensitivity by patterning a piezoresistive strain sensor with an enhanced sensitivity by patterning
the AgNWs into electrodes with an interdigitated shape. The fabricated strain sensor had ~1.57 GF at 30% strain, which was much higher than the sensitivity of typical parallel-plate-type capacitive strain sensor. In addition, the enhanced sensor had no hysteresis until the ε value was 15% and showed stable and reliable sensing performance during the cyclic stretching test at ε values of 10% for 1000 cycles.

Various nanomaterials such as ZnO NWs [195], PVDF NWs [199] and BaTiO3 NPs [70] have been used to develop piezoelectric wearable strain sensors. Chen et al. [70] reported an innovative wearable strain sensor. A composite of piezoelectric BaTiO3 NPs and PDMS was adopted as the sensing layer, which was sandwiched in the two sprayed AgNWs transparent electrodes. The developed wearable sensor exhibited good transparency, mechanical flexibility and stretchability. This highly flexible wearable sensor afforded a strain-sensing range up to 60% strain based on piezoelectric mechanism, which was attached to the human body for real-time health monitoring such as eye blinking, pronunciation, arm movement, and BP pulse wave.

C. Electrophysiological Sensors

A major class of wearable sensors used in health applications is electrodes that sense electrophysiological signals. Electrophysiological signals or electrographic modalities such as ECG [200–203], EEG [204], and EMG [205–207] defined by body part are commonly in clinical use, which are relevant to point-of-care for remote chronic disease care [19]. EMG is a powerful electrodiagnostic medicine technique that plays an important role in recording the electrical activity produced by skeletal muscles, evaluating the health of the muscle tissues and nerves, and diagnosing to identify neuromuscular diseases and disorders of motor control. EEG is an electrophysiological monitoring method to record the electrical activity of the brain, which is often applied to diagnose epilepsy that causes abnormalities in EEG recordings, and focal brain disorders (e.g., tumors and stroke). ECG is the process of recording the electrical activity of the heart using wearable electrodes placed on the skin, which represents one of the most commonly used tools to diagnose and manage cardiovascular diseases. Wearable electrophysiological sensors that can continuously monitor those electrographic modalities will greatly promote their applications in diagnosis and rehabilitation for remote healthcare. However, the commonly used pre-gelled (wet) electrodes in the wearable electrophysiological sensor are unsuitable for continuous measurements. For example, the standard commercial Ag/AgCl sensing electrode relies on a conductive gel to maintain good electrical contact with the skin, but the gel will dry over the time, leading to drastically deteriorated signal quality and repeated reapplication of new gel electrodes. Moreover, the gel can provoke dermal irritation and even allergies of the patient’s skin, which causes excessive discomfort, especially in long-term wearing. In addition, sweat between the wet sensing electrodes and skin provides another source of signal degradation for wearable electrophysiological sensors [205]. Compared with dry electrodes, wet electrodes are inconvenient and sometimes infeasible. Owing to the mechanical and electrical versatility of nanoscale forms, various nanomaterials have rapidly been applied to wearable electrophysiological sensors, replacing traditional gel-based electrodes in next-generation wearable healthcare. Gel-free (dry) wearable electrophysi-ological sensors can seamlessly integrate with soft and curvilinear human skin and worn for long-term while maintaining high signal quality without provoking skin allergies. Some substantial efforts, which have been devoted to researching and developing nano-based gel-free (dry) wearable electrophysiological sensors, are summarized in Table V.

Kang et al. [101] demonstrated all-solution-processed CNT-based dry electrodes for the recording of ECG and EMG signals, which were directly attached to the human skin such as the forearm. The key parameters of ECG signals were clearly extracted by such sensing electrodes, which shown comparable function with conventional Ag/AgCl wet electrodes. Furthermore, the sensing performance of CNT-based dry electrodes was maintained after the bending test of 200 cycles, which was essential for wearable electrophysiological sensors in a non-invasive method for health monitoring. Kim et al. [95] presented a highly conformable, stretchable, and transparent electrode for application in electrophysiological sensors based on PDMS and AgNWs networks. After adding a small amount of a commercially available nonionic surfactant (Triton X), PDMS became highly adhesive and mechanically flexible and stretchable. AgNWs were embedded in the adhesive PDMS (aPDMS) matrix to obtain aPDMS-based transparent sensing
electrodes with the highly enhanced conformability and stretchability for the recording of ECG signals. Their wearable ECG sensors exhibited significantly improved usability compared with the bare PDMS-based sensors because of the better adhesiveness and conformability to the human skin. Fondjo et al. [205] introduced a flexible wearable electrophysiological sensor based on elastomeric hybrid nanocomposite composed of CB, CNTs, AgNWs and PDMS. Those materials were chosen because of their good electrical conductivity and different length scale to provide continuous conductive paths in the nonconductive PDMS substrate. The nanocomposite was tested over 5, 10 and 15 hours to investigate the electrical stability and the sensing performance of the developed electrode during EMG signal recording. Lee et al. [204] fabricated a CNT/aPDMS based dry EEG electrode for measuring of EEG signals [Fig. 13(a)]. The developed CNT/aPDMS electrode exhibited high flexibility, good conductivity, and enough adhesiveness to be capable of making conformal contact with a hairy scalp. The sensing electrodes were evaluated by recording EEG signals and confirmed that the developed electrodes provided a high SNR with good tolerance for motion, which were comparable to conventional wet electrodes.

D. Electrochemical Sensors

1) Body Fluids Analysis: Wearable electrochemical sensors are essential to the realization of personalized chronic disease care by continuously sampling human body fluids, which are rich in biomedical information and could enable non-invasive monitoring [12]. With the demand for potential applications in disease diagnosis and personal healthcare, wearable electrochemical sensors have been widely used to detect various biological indicators, such as pH values [208], electrolytes (e.g., Na⁺ and K⁺)[12], metabolites (e.g. uric acid and urea) [99] and biochemicals (e.g., glucose and lactate) [76] etc. [209]. These indicators are detected through body biofluids including sweat, tears and saliva etc., which can alert patients from dehydration, fatigue, and early disease symptoms. Combining the advantages of wearable technology with electrochemical tech-
TABLE VI
SUMMARY OF TYPICAL WEARABLE ELECTROCHEMICAL SENSORS FOR BODY FLUIDS ANALYSIS

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Materials</th>
<th>Biofluids</th>
<th>Flexible/Stretchable</th>
<th>Stability</th>
<th>Analytes</th>
<th>Detection limit</th>
<th>Resolution/Sensitivity</th>
<th>RSID</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>[99]</td>
<td>ZnO nanoarrays</td>
<td>Sweat</td>
<td>Yes/No</td>
<td>800 times bending</td>
<td>Lactate 0.1 nM/L</td>
<td>0.1±0.05 nM/L</td>
<td>–</td>
<td>0–20 nM/L</td>
<td></td>
</tr>
<tr>
<td>[78]</td>
<td>CuO NRs</td>
<td>Sweat/Tears</td>
<td>Yes/No</td>
<td>–</td>
<td>Urea 0.5 mM</td>
<td>0.5±0.2 mM</td>
<td>–</td>
<td>5–25 nM/L</td>
<td></td>
</tr>
<tr>
<td>[76]</td>
<td>ZnO nanocombs</td>
<td>Sweat</td>
<td>Yes/No</td>
<td>pH 4–8</td>
<td>Glucose 0.1 nM/mL</td>
<td>–</td>
<td>–</td>
<td>0.01–200 mg/dL</td>
<td></td>
</tr>
<tr>
<td>[209]</td>
<td>Ag NPs</td>
<td>Saliva</td>
<td>Yes/No</td>
<td>–</td>
<td>Hydrogen peroxide (H₂O₂) 13 μM</td>
<td>35.97 ± 7.2 μA/mM</td>
<td>–</td>
<td>20 μM–33 mM</td>
<td></td>
</tr>
<tr>
<td>[82]</td>
<td>CNTs</td>
<td>Sweat</td>
<td>Yes/No</td>
<td>–</td>
<td>Caffeine 3x10⁻⁵ M</td>
<td>110 ± 30 nA/mM</td>
<td>–</td>
<td>10 μM–40 mM</td>
<td></td>
</tr>
<tr>
<td>[12]</td>
<td>CNTs</td>
<td>Sweat</td>
<td>Yes/No</td>
<td>60 times bending</td>
<td>Lactate –</td>
<td>2.35 ± 0.20 mM</td>
<td>–</td>
<td>0–200 μM</td>
<td></td>
</tr>
<tr>
<td>[98]</td>
<td>InO₃ nanoribbon</td>
<td>Sweat/Tears/Saliva</td>
<td>Yes/No</td>
<td>100 times bending</td>
<td>Na⁺  6.42 mV/mM</td>
<td>–</td>
<td>–</td>
<td>10–160 mM</td>
<td></td>
</tr>
<tr>
<td>[77]</td>
<td>MWCNT</td>
<td>Sweat</td>
<td>Yes/Yes</td>
<td>200 times bending</td>
<td>Glucose 0.05 mM</td>
<td>288.86 ± 1.05 μA/mM</td>
<td>–</td>
<td>0–5 mM</td>
<td></td>
</tr>
<tr>
<td>[208]</td>
<td>InO₃ nanofoil</td>
<td>Tears</td>
<td>Yes/No</td>
<td>–</td>
<td>pH –</td>
<td>8.6 ± 5.2 μA/pH</td>
<td>–</td>
<td>pH 5.5–9</td>
<td></td>
</tr>
</tbody>
</table>

TABLE VII
SUMMARY OF TYPICAL WEARABLE ELECTROCHEMICAL SENSORS FOR BREATH GAS ANALYSIS

<table>
<thead>
<tr>
<th>Active Materials</th>
<th>Substrate</th>
<th>Sensitivity</th>
<th>Range</th>
<th>Flexible/Stretchable</th>
<th>Stability (bending cycles)</th>
<th>Response capability</th>
<th>Applications</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-layer graphene</td>
<td>PET</td>
<td>–</td>
<td>0.03–0.1 ppb NO₂, 0.04–0.1 ppb ammonia (NH₃)</td>
<td>Yes/No</td>
<td>70</td>
<td>2 s, 1 s</td>
<td>Health monitoring</td>
<td>[210]</td>
</tr>
<tr>
<td>WO₃ NPs</td>
<td>PI</td>
<td>–</td>
<td>1.88 ppm NO₂</td>
<td>Yes/No</td>
<td>4x10⁷</td>
<td>17 s</td>
<td>Public safety, human healthcare, and environmental conditions</td>
<td>[211]</td>
</tr>
<tr>
<td>SrGeO₃ NTS</td>
<td>PET</td>
<td>2.54</td>
<td>100 ppm NH₃</td>
<td>Yes/No</td>
<td>7</td>
<td>25 s</td>
<td>Health monitoring, personal safety protection, and industrial manufacturing</td>
<td>[212]</td>
</tr>
<tr>
<td>ZnO NPs</td>
<td>Cotton fabrics</td>
<td>33, 9 and 16</td>
<td>100 ppm of acetaldehyde, ethanol and NH₃</td>
<td>Yes/No</td>
<td>–</td>
<td>228 s, 39 s and 50 s</td>
<td>Protection against environmental and health hazards</td>
<td>[213]</td>
</tr>
<tr>
<td>PANI NFs</td>
<td>Respirator</td>
<td>5.8 and 16.4</td>
<td>25–100 ppm NH₃</td>
<td>Yes/No</td>
<td>10³</td>
<td>13 s</td>
<td>Biomedical diagnosis</td>
<td>[214]</td>
</tr>
<tr>
<td>AuNPs</td>
<td>PI</td>
<td>3.5x10⁻⁴ ppm⁻¹</td>
<td>200–800 ppm ethanol</td>
<td>Yes/No</td>
<td>11</td>
<td>–</td>
<td>Human health monitoring</td>
<td>[215]</td>
</tr>
</tbody>
</table>
be applied to wearable healthcare electronics.

2) Breath Gas Analysis: Wearable electrochemical sensors for breath gas analysis, also called gas sensors, are among the most important technologies in our daily life and have attracted considerable research attention because of their potential application in chronic disease care. For instance, numerous experimental data have also verified that the amount and/or species of volatile organic compounds (VOCs) in the exhaled breath are closely related to some metabolic diseases [41]. Continuous detection of the specific VOCs provides a promising approach for the non-invasive and remote healthcare monitoring of metabolic diseases and pre-diagnosis. This expands the scope of potential applications. To achieve the high reliability of wearable gas sensors, these requirements must be addressed. The summary of recent typical wearable gas sensors with key performance indicators is shown in Table VIII.

In recent years, several teams have developed different kinds of wearable gas sensors using various nanomaterials, such as CNTs, AuNPs [210], graphene, metal oxide NWs [211], [212], [213] and polymer nanocomposite [214], [215]. Parikh et al. [216] have reported a flexible gas sensor of CNTs on a cellulose substrate fabricated by inkjet printing. The flexible gas sensor showed excellent selectivity and stability in the detection of aggressive vapors, such as nitrogen oxides (NOx). However, their 5 min response time was too slow for practical sensing applications. For most flexible gas sensors operating at room temperature, the response and recovery times limit their practical application in wearable electronics. Recently, wearable gas sensors have been widely used in non-invasive healthcare. Tracking disease status relies on the detection of VOCs exhaled by the body. Kahn et al. [217] reported a respiratory diagnostic array based on AuNPs. These devices were used to examine ovarian cancer in real breath samples from 43 volunteers with ovarian cancer and control experiments. In their study, ovarian cancer has been successfully located, which further confirms that the sensor array can specifically identify the disease by analyzing the collected respiratory data. Wang et al. [218] reported a streamlined strategy to design a multifunctional biomaterial that mimics the surface morphology of natural butterfly wings and added the functional properties of graphene. Based on the ultra-fast response speed (1 s) and the lower detection limit (20 ppb), the nanocomposite was integrated into a proof-of-concept wristband for real-time monitoring of diabetes-related acetone vapors. More importantly, humidity had almost no effect on acetone sensing performance, which was important for acetone detection of exhaled gases [Fig. 14(b)].

E. Temperature Sensors

Body temperature is one of the vital signals, which is closely related to various types of illnesses/diseases (e.g., heat stroke, congestive heart failure, infection, fever or chills, hyperthermia), physiological status of human body (e.g., skin moisture content, tissue thermal conductivity, blood flow status, and wound healing). Typically, the transduction mechanism of the wearable temperature sensor is the thermoresistive effect. Significant efforts have been devoted to taking advantage of nanomaterials to enhance sensing performance, such as graphene [62], CNTs [219], [220], CNFs [221], AgNPs [64], metal oxide NWs [49]. The summary of recent typical wearable temperature sensors with key performance indicators is shown in Table VIII.

Hong et al. [222] prepared a SWCNT thin film transistor, stretchable PANI NFs wearable temperature sensor active matrix showing a high resistance sensitivity of 1.0% °C with a response time of 1.8 s in the range of 15–45 °C and stable at 30% of biaxial stretching. Oh et al. [94] demonstrated a highly sensitive wearable temperature sensor with a bioinspired octopus-mimicking adhesive, which was consist of a composite of poly(N-isopropylacrylamide) (pNIPAM), PDMS and CNTs, as shown in Fig. 14(a). This temperature sensor had an extremely high thermal sensitivity of 2.6% °C between 25 and 40 °C, which made it capable of accurately detecting a skin temperature change of 0.5 °C. Moreover, the fabricated sensor showed good stability and reproducibility for the detection of skin temperature under repeated attachment/detachment cycles onto the skin without any skin irritation for a long time. Aziz et al. [219] fabricated a textile-based temperature sensor using a composite of SWCNT-filled PVD/PEDOT:PSS, which were capable of a highly linear and stable response for a wide range of temperatures (25–100 °C) and a sensitivity of 38 kΩ/°C.

F. Multifunctional Sensors

Non-invasive wearable sensors for chronic disease care provide a long-term continuous record of human activities. The acute body response can be used for preventive medicine, disease diagnosis, patient prognosis monitoring and geriatric care, which require a wearable sensor that can detect not only a single signal but also multiple signals at the same time. Multifunctional sensors that can simultaneously detect multiple stimuli are highly desired in chronic disease care. For example, detecting pulse pressure and temperature of artery vessels at
once can be used to analyze the influence of temperature on the pulse pressure [49]. Recently, researches on multifunctional sensors with nano-based enhancement have begun to emerge. Suen et al. [46] developed a novel multifunctional tactile sensor to mimic human skin with high force sensitivity, high flexibility, and temperature measurable performance based on interlocked structures and high-aspect-ratio zinc NRs grew vertically on the PDMS surface. Moreover, this sensor was applied for measuring and monitoring arterial pulse pressure. Xu et al. [223] developed a multifunctional wearable sensor based on a rGO film and a porous inverse opal acetyl cellulose (IOAC) film. This sensor could simultaneously monitor various analytes’ concentrations in sweat and track the different large human motions in situ, as shown in Fig. 14(d). The rGO film was used as a strain-sensing layer for human motion detection based on piezoresistive mechanism, while the porous IOAC film was used as a flexible substrate not only for highly sensitive motion sensing but also for the collection and analysis of sweat through colorimetric changes or reflection-peak shifts. The developed sensor exhibited a wide sensing range of NaCl concentrations in sweat from normal 30mM to 680mM under the conditions of severe dehydration. Lee et al. [224] implemented a graphene-based wearable sensor that can detect temperature, humidity and various forms of strain simultaneously, and was equipped with a heater to regulate body temperature. Jovay et al. [12] provide a mechanically flexible, fully integrated sensor array for multiplexed analysis of sweat while selectively measuring glucose and lactate metabolites, sodium and potassium electrolytes, and skin temperature. Wang et al. [221] fabricated a coupled temperature-pressure wearable sensor by assembling a temperature sensor and a strain sensor in a single platform, both of which were made of flexible and
transient silk-nanofiber-derived carbon fiber membranes (SilkCFM), as shown in Fig. 14(c). The temperature sensor presented a high thermal sensitivity of 0.81% \(^{-1}\). Meanwhile, the strain sensor exhibited an extremely high sensitivity with a GF of \(\sim 8350\) at 50% strain, which was capable of detecting subtle pressure induced by local strain. Most importantly, the structure of the SilkCFM in each sensor was designed to be independent of each other stimuli. Thereby, the integrated multifunctional wearable sensor simultaneously and accurately detected temperature and pressure without extra decoupling. It was verified that the developed multifunctional sensor could monitor breathing, finger pressing, and spatial distribution of temperature and pressure on the human body. Ho et al. [63] developed a transparent and stretchable graphene-based multifunctional sensor by integrating three different sensors into a single platform, enabling the detection of humidity, thermal, and pressure at the same time. Importantly, there was no signal coupling among the sensing data from each sensor. The conductive electrodes and interconnects for three sensors were made of graphene. The active sensing materials of humidity and temperature sensors were GO and rGO, respectively. The capacitive pressure and strain sensors adopted a typical sensing structure constructed by sandwiching the top PDMS between two graphene electrodes. Furthermore, the multifunctional sensor could monitor various sensations in human daily life, such as breathing and finger pressing, with an excellent sensitivity.

VI. CHALLENGES AND DIRECTIONS

For the biomedical application, the sensor with flexible or stretchable features has the capability to conform to the skin or tissue well. Numerous advanced wearable sensors have been researched and developed, which have shown promising potential in a broad range of chronic disease care we presented in Section 1. It should be noticed that sensor performance may be degraded when the sensor is under stretching and bending. To make the sensor applied in real biomedical application, the sensor should maintain their performance and reliability in the first place rather than super flexibility/stretchability features [89], [225]. Despite the exciting progress in Section and Section 1, there remain many challenges and opportunities associated with sensing performance, manufacturing and materials. From the state of the art, there are several new trends in the researches and applications of the flexible and stretchable sensor. This section will summarize and discuss the current critical issues and future directions of wearable sensors as well as their new trends in applications.

A. Scientific Challenges

1) Sensor Characteristics:

In the past few years, various types of wearable sensors have been rapidly developed and made great progress [226], [227]. These advanced innovations confirm that wearable sensor with nano-based enhancement for flexibility and stretchability has potential scope in the field of chronic disease care. However, there is still a long way to go to apply the developed wearable sensors to chronic disease care.

a) Tactile/Pressure sensors: Ultrasensitive wearable tactile/pressure sensors can measure subtle pressure such as BP pulse wave tracking, which can provide important information about cardiac health status. At present, there are many sensing mechanisms of flexible tactile/pressure sensors, each of which has its own advantages and drawbacks. For example, the greatest advantage of piezoresistive is the fast response and good dynamic performance. Due to the characteristics of the piezoresistive material itself, it has relatively serious hysteresis characteristics and low repeatability. The structure and measurement principle of capacitive sensors are relatively simple, easy to implement, and have good sensitivity for lower pressure detection but are also limited by its own sandwiched structure. Capacitive pressure sensors are sensitive to electromagnetic interference and parasitic capacitance. However, the capacitance under stretching is not stable because of the Poisson’s ratios of the materials that change the dielectric thickness and the distance of two electrodes during stretching [193]. The corresponding detection circuit is also complicated. Piezoelectric sensors have good stability and are suitable for dynamic measurement, but are prone to crosstalk, drift. Due to the relatively weak piezoelectric effect, a signal amplifier is required. Certain intrinsic characteristics of different sensing mechanisms limit the applications of pressure/tactile sensors. How to balance these advantages and disadvantages to achieve the best performance is one of the most difficult challenges in the research of flexible pressure/tactile sensors. Moreover, great challenges still remain in developing flexible and stretchable pressure/tactile sensors with high sensitivity in response to low-level pressures (<1 kPa) that are common in sensing chronic disease indicators [115]. In addition, the underlying mechanisms that causes fluctuation in sensor performance is not well investigated, and new material strategies that provide high repeatability remain to be developed [86]. The main technical challenge related to all these pressure sensor technologies is related to the motion artifacts. For example, moving of the arm and dangling wires naturally create noise to the system. To minimize motion artifacts, the flexible sensor must maintain robust, intimate contact with the human body during movement [36], [228]. Motion artifacts are generally distributed in the low frequency band (0–5 Hz) [96]. Liu et al. [136] designed a high-pass filter (cutoff frequency, 15 Hz) in the sensing circuit to remove motion artifacts. Signal processing can be used to tackle some of these issues [20], [105]. But, for designing of the sensors, it means high sensitivity with the large dynamic region [229]. Yao et al. [38] integrated ECG sensor with a highly stretchable capacitive strain sensor to monitor arm motion for mitigating the motion artifacts in ECG signals.

b) Strain sensors: Due to the similar sensing mechanisms as the tactile/pressure sensors discussed above, wearable strain sensors also face the challenge of balancing the advantages and disadvantages of different types of strain sensors. Additionally, the integration capability of a single versatile strain sensor for low strain detectability (such as the strain of artery pulses as small as 0.1%), high stretchability (such as the strain of body movement as large as 100%), ultra-high sensitivity, adjustable sensing ranges, and thin sensor size remains a challenge [185]. The combination of novel sensing nanomaterials and the design of the geometric sensing structure are expected to be effective approaches to address these challenges [185]. Up to now, various approaches have been proposed to fabricate wearable strain sensors with high flexibility and stretchability by com-
bining conductive nanomaterials with elastic polymers. However, most of the reported wearable strain sensors failed to simultaneously achieve high sensitivity and high stretchability [See Table ], which limits their applications in monitoring human body motions for chronic disease care [90].

c) Electrophysiological sensors: Traditional wet or gel-based sensing electrodes cause skin irritation and gradual decrease of conductivity due to drying of gel over a short duration, leading to degradation of signal quality. In addition, wet/gel-based interfacing suffers from severe contact noise [230]. To overcome these drawbacks, many significant efforts have been devoted to the flexible and stretchable dry electrodes that have the potential for long duration sensing and ease of use. However, there are a number of challenges that need to be addressed including low impedance surface contact, signal quality, biocompatibility, skin breathing or gas permeability [231]. The low impedance sensing electrode has the possibility of reducing the contact noise during recording of the electrophysiological signals [230]. Most studies have focused on the flexible and stretchable dry electrodes by mixing conductive nanomaterials with an elastic polymer such as CNT/PDMS-based wearable electrophysiological sensors. However, it is very difficult to avoid the deterioration in the conductivity of electrodes, resulting in the degradation of the overall sensing performance of wearable electrophysiological sensors [101]. Most recently, Miyamoto et al. [232] presented a novel approach to fabricate highly gas-permeable, ultrathin, lightweight and stretchable sensors. This technology is based on nanomesh fabricated by electrospinning of polyvinyl alcohol (PVA) and deposition of Au electrodes using a shadow mask. The technology enables transferring of electrodes directly on-skin. In the future, the technology could be beneficial for other sensors as well.

d) Electrochemical sensors: Body fluids and breath gas contain tremendous biochemical analytes that can provide tremendous information and are more easy to access. Current studies have shown simultaneous detection of multiple analytes using wearable electrochemical sensors. However, wearable non-invasive electrochemical sensors both in the commercial and research area can primarily detect one analyte over a period of time and thus multiplexing is still a challenge in the development of electrochemical sensors [76]. In addition to multiplexing, many challenges also exist for the accuracy of sensors in body fluids and breath gas. For example, the recent studies suggest a wearable diagnosis device based on the glucose concentration in sweat to estimate blood glucose levels. The glucose concentration in sweat is much lower than the glucose level in blood. What’s more, the sensing readings can be easily affected by the changes in environmental temperature, mechanical deformation caused by human body motion, and the sampling procedure [98].

e) Temperature sensors: Currently, most of the developed flexible and stretchable sensors exhibit enough sensitivity and resolution of $\approx 0.1 ^\circ C$, enabling their application in the daily health monitoring. However, there are some essential requirements for chronic disease diagnosis, such as a higher sensitivity with an accuracy of 0.01°C for precise detection under dynamic body motion, high-resolution temperature distribution using sensor arrays or networks [6]. In order to eliminate the need of amplifier, the sensitivity of the polymer-based sensors has been significantly enhanced. However, most of the polymer-based sensors have a very narrow temperature sensing range, which cannot satisfy the requirement for the measuring of human body temperature. Furthermore, there are still many great challenges to improve the accuracy, reduce response time, enhance the reproducibility of resistivity and diminish the hysteresis of the polymer-based temperature sensors [6]. Besides, a sophisticated electronic circuit is always in demand for accurate detection to minimize the effect of changeable conductors on flexible substrates, making it difficult for integration and wearable applications [6].

2) Manufacturing:

In addition to sensor characteristics, there are still challenging issues for implementing wearable sensors in chronic disease care. For instance, many of the flexible and stretchable wearable sensors thus far involve complicated or cumbersome fabrication processes, such as multiple cycles of coating, photolithography or photoetching techniques, and metal evaporation [24]. Moreover, since most wearable sensors are composed of metal-based micro/nano structures and hybrid composites with nanomaterials (such as metallic NWs and graphene sheets), the fabrication process requires high temperature (such as chemical and physical vapor deposition), electroplating, and delicate transfer processes [92]. Generally, flexible micro-nanostructured substrates are used for the fabrication of high-sensitivity wearable sensors with a low detection limit. Nevertheless, the fabrication of micro- or nanostructures usually is rather complicated and time-consuming [47]. In addition, delicate transfer processes are always complex, which include coating nanomaterials on rigid substrates such as wafers or glasses, embedding the films of nanomaterials into elastomeric materials (such as PDMS and PU), and removing the rigid substrates. These processes are inefficient due to the additional rigid substrate and transfer process that cannot be repeated on the same substrate. Thus, the multilayered and complex structures required in the commercial wearable electronics are unattainable [193]. Besides, wearable sensors having multiple stacked layers for multifunctional sensing are not sufficiently flexible and stretchable for conformal contact against nonplanar body surface [92]. To obtain the function of multi-sensing, the sophisticated fabrication process and the structural complexity of wearable sensors are hindering their practical applications [49]. Additionally, wearable sensors with ultrathin films are difficult to handle and attach to the skin. Assembling other components on ultrathin substrates, such as a signal processing circuits and batteries, without sacrificing the conformability owing to the advantage of thickness remains challenging [42]. Furthermore, another stringent requirement for wearable sensors is the low power consumption, however, manufacturing flexible power supplies with high power densities remains a challenge [47]. To address the above challenges, printing, as a solution-based process for patterning flexible and stretchable electronics, is a powerful technique to enable the production of large-scale, low-cost wearable sensors [159], [233]. However, different printing methods have their own limitations and technical challenges. For example, contact printing methods such as gravure printing and screen printing have been reported for printing flexible and stretchable electrodes used in wearable sensors. Although these methods ena-
ble efficient and large-scale printing, the resolution and the conductivity of the electrodes are typically limited [159]. Moreover, non-contact printing technologies such as inkjet printing allowing on-demand patterning are more advantageous than contact printing. However, inkjet printing of long metallic NWs (typically >10 μm) is a significant challenge because of the high risk of nozzle clogging during the printing process and the difficulty in maintaining the integrity of the printed pattern. The resolution of inkjet printing technology is primarily limited to the size of the nozzle, which is comparable to the size of the printed droplets related to the process parameters. Although the droplet size can be adjusted by optimizing the inkjet printing process parameters, this method cannot achieve enough high resolution for the advanced medical application. In order to minimize the risk of nozzle clogging, the size of the particles in the functional ink is suggested not to exceed 1/100 times the diameter of the nozzle, as a general “rule of thumb” [159].

Considering the length of general 1D nanomaterials (>10 μm), it is extremely difficult for inkjet printing to obtain high-resolution patterns. Although some research of applying inkjet printing on printing metallic NWs has been done in recent years, the resolution is generally sub-millimeter, which is far from the requirements of advanced electronics for healthcare [159]. EHD printing, as an emerging technology, provides high-resolution printing by producing droplets that are much smaller than the nozzle diameter. Thanks to this unique capability, a nozzle with a large diameter can be used in EHD printing to produce more subtle patterns and also evade the dilemma of high resolution and nozzle clogging during printing [159]. However, the printing process involves multiple physical quantities in the electric and fluid field, which means that the printing process is complicated and it is not easy to guarantee the stability of the printing.

3) Materials:
Many materials are feasible to fabricate wearable sensors for long-term and precise chronic disease care. Numerous existing researches are conducted on flexible and stretchable conductors. The flexible and stretchable conductors consist of two essential components: 1) conductive elements and 2) flexible and stretchable substrates. Nevertheless, there are many technical challenges in material science, which should be addressed to develop advanced wearable sensors for chronic disease care.

a) Conductive elements: In order to attach wearable sensors to complex and non-planar body surfaces under complicated deformations (such as bending, stretching and twisting), nanomaterials are suitable candidates for conductive elements because of their predominant flexibility compared to traditional metallic conductive materials [133]. A variety of low-dimensional conductive nanomaterials such as conducting polymers, carbon-based nanomaterials, metallic NWs, conductive NFs, and graphene are beneficial to achieve high sensitivity. Among these nanomaterials, metallic NWs could be very promising candidates for conductive elements in flexible and stretchable conductors. However, the high price hinders metallic NWs large-scale applications [133]. Moreover, most of the wearable sensors based on metallic NWs has required a complex transfer process [193]. Furthermore, most metallic NWs are susceptible to oxidation in an ambient environment over a long-term working [231]. Some conductive NFs are difficult to be prepared and handled during the fabrication of wearable sensors [47]. By contrast, large-scale and low-cost carbon-based nanomaterials exhibit excellent stability in ambient environments, which could be prepared through the well-established chemical vapor deposition process [47]. In addition, carbon-based nanomaterials exhibit outstanding mechanical, electrical and thermal properties, enabling to build blocks of novel multifunctional materials for wearable sensors. Incorporating carbon-based nanomaterials in composite materials can increase strength and reduce the weight of materials compared to the carbon fiber-reinforced polymer composites [234]. However, the instability and relatively low electrical conductivity of conductive polymers and carbon-based nanomaterials have become major limiting factors in their performance and application [133]. Although nanomaterials are generally interested by scientists, we should also look carefully on microsized particles like Ag [235] or carbon [236], [237] flakes. These materials are used to produce screen printable inks that can stand high elongations. The stretchability is not so high that in case of some nanowires, but the total resistance is in much lower level. Furthermore, the fabrication process is much more simplified and cost-effective.

b) Flexible and stretchable substrates: PDMS is a good candidate for flexible and stretchable substrates discussed in Section . Although PDMS possesses so many superior properties, the weak interfacial adhesion leading to instability between PDMS and conductive elements is still a challenge constraining its applications in wearable sensors. The superhydrophobicity of its surface and rapid recovery from hydrophilic to the hydrophobic surface after treatment by oxygen plasma are major inducements of weak interfacial adhesion [133]. Even worse, the conductive elements deposited on its surface could be peeled off easily when an external force is applied. Therefore, the PDMS substrates should have sufficient interfacial adhesion force with the conductive elements to manufacture advanced wearable sensor [90]. With the purpose of enhancing adhesion between the various conductive elements and PDMS, numerous methods have been adopted, such as surface functionalization and in situ polymerization [133]. However, the process of chemical modification is quite complicated and difficult to control [133]. Hence, a facile, cost-effective, and scalable interface modification method to enhance the adhesion of conductive elements on or in a flexible and stretchable PDMS substrate is still a challenge. Compared to PDMS, EcoFlex is a translucent but is much more flexible and stretchable elastomer with a Young’s modulus of about 60 kPa [238]. EcoFlex is also prepared by mixing a precursor and a crosslinker. Wearable sensors made of the carbon-based Ecoflex nanocomposite will possess high performance characteristics due to strong interfacial adhesion force between the active material and the Ecoflex matrix [239]. As compared to the aging effect of PDMS, Ecoflex is suitable for long term sensing applications because of its water resistivity [239]. Similar to PDMS, a major disadvantage EcoFlex is low adhesion to metallic materials, limiting the fabrication of electrical interconnects on the surface [238]. Other widely used wearable electronics substrate material is PU. The advantage is suitability to printed electronics fabrication and good adhesion to many commercially available materials. Furthermore, PU is widely used in the textile application and enables seamless integration of electronics using heat pressing. In addition to silicone rubber
and polymer, textiles represent a promising class of substrates for implementing wearable sensors. Because of the impressive performance of textile (e.g., high surface area, lightweight, good elasticity, high strength and good tear resistance), many prototypes of wearable sensors based on fiber/textile have been reported. The most fabrication methods of textile-based wearable sensors are coating, printing or laminating functional materials (CNTs, graphene and metal NWs, etc.) onto cloth fibers or fabrics [156]. However, these deposition approach may impair the flexibility of the fabrics, especially when the deposited metallic materials [84], [240]. Furthermore, it is difficult to apply conventional printing methods to textiles in some cases, since functional ink tends to permeate the textile, resulting in blurring of pattern [156]. Another promising method to realize a textile-based wearable sensor is to knit or weave functional fibers with other conventional yarns into device without complicated process [113]. However, the surface roughness of fiber is typically on the order of microns, which is not compatible with conventional integrated circuit technology [155], [240]. Therefore, integration of the textile-based component with other electronic parts is still a challenge. For sensing performance, the sensors from knitted structured fabrics have response fluctuations and hysteresis due to the inelastic deformation ability and inevitable poor elasticity recovery, which limit their applications [86]. If the desired features of wearable sensor include low cost, simple hardware requirements and reusability, the state of the art of textile-based ones is far below requirements for practical biomedical applications [79]. Additionally, the wearable sensor is undergoing a process of changing towards fully flexible and stretchable. Another challenge about that process is associated with the heterogeneous integration of flexible/stretchable wearable sensors with other, typically stiffer, components such as displays, data processing and transmission units or batteries. Due to the dissimilar electrical/mechanical/thermal properties, interfaces between the wearable sensors and these other rigid components often lead to cracking and peel-off damaging under repetitive mechanical deformations and invalidate the sensor.

B. Research Directions

Personalized chronic disease care and early diagnosis, combined with disease prevention, have gained increasing attention. Effective and precise chronic disease care and early diagnosis rely on uninterrupted monitoring and access of personal health data. To achieve this goal, more attention have been paid to the wearable sensors that can be directly mounted on the human body, because they can obtain the patients’ health data in real time, uninterruptedly, and non-invasively [41]. Driven by the increasing demand for chronic disease care and wearable devices, multifunctional, self-powered and textile-based wearable sensors are attracting great interest as future research directions.

1) Multifunctional Wearable Sensors: Various wearable sensors based on different nanomaterials and structures have been rapidly developed to monitor different health parameters such as skin temperature, electrophysiological signals, chemical analytes in the body fluids and breath gas. Considering that some health signals, such as analytes in sweat and body temperature, strongly depend on the human motion [223], a single parameter is insufficient to fully assess the health condition of the patients, let alone the diagnosis or prediction of chronic disease [41]. Thus, there is a new trend to develop multifunctional wearable sensors for simultaneous monitoring of the multiple health signals, which becomes more significant [41]. Various sensing functions (such as the sensations of temperature, pressure and strain) that are responsive to different kinds of stimuli are the kernel of wearable multifunctional sensors, enabling to provide smart sensing functions of physiological detection, like chronic condition monitoring, disease diagnosis, and therapy [6]. For example, the treatment of chronic homeostasis-related diseases such as diabetes mellitus can be carried out by continuous point-of-care monitoring of biomarkers based on electrochemical sensing with real-time physical sensing [224]. Pioneer works have tried to develop wearable multifunctional sensors through multi-sensing materials in a single sensor or the parallel integration of multiple different sensors on a single platform. Although the former approach has an obvious advantage in the development of compact, multifunctional and simplified wearable sensors, they usually give coupled response signals. It is difficult to decouple these combined signals, which limits their practical application in chronic disease care [41]. Each sensor in the latter approach is responsive to a defined stimulus, which efficiently solves the coupled signal issues of single wearable sensor based on multifunctional sensing materials [41]. However, it is not straightforward to enable the sensation and discriminate among multi-source external stimuli. The fabrication of such multifunctional sensors typically involves heterogeneous substrates and sophisticated electrical interconnections or signal processing circuits, which often causes signal interference among different sensors [6]. Hence, it also suffers the impair of coupled signal, which can be minimized by advanced manufacturing. Recent efforts in developing multifunctional wearable sensors generally confront with limitations, such as the interference of different sensors, the sophisticated structural and circuitual design, and the complicated high-cost fabrication [221].

2) Self-Powered Wearable Sensors: In the future, wearable sensors will be ubiquitous in our daily life, which inevitably brings insatiable demands on the power supply. Meanwhile, wearable sensors with multifunction and the need for long-term uninterrupted health monitoring require large increases in power consumption. In addition, since the demand for the number of sensors has increased to achieve precise health monitoring, self-powered wearable sensors operating without an external power source have attracted widespread interest. Mechanical energy and thermal energy is the most desirable sources that can be consistently and unconsciously collected during wearing without being limited by time or location. Despite significant advances in the development of practical wearable sensors, additional bias voltages must be applied to most wearable sensors through external power supplies, which will cause issues such as power consumption and structural complexity [6]. To tackle the issue of power supply, it is increasingly important to obtain tiny but useful mechanical/thermal energy from the human body to satisfy energy requirements [199]. In addition to energy-harvesting self-powered sensors from mechanical energy and thermal energy, integration with flexible energy storage devices like supercapacitor can also be an attractive solution [157], [168]. Major advantages of supercapacitor are fast charge/discharge.


rates, high power densities, and long cycle lives (thousands to millions of cycles) [241]. To ensure the wearability of integrated wearable sensors, supercapacitors should have additional features including high-flexibility, light-weight, and wider operation temperature range [241]. Hence, an integrated wearable sensor with flexible and stretchable energy harvesting, conversion and storage units is another important research trend for chronic disease care.

3) Textile-Based/Fiber-Shaped Wearable Sensors: Although advances have been made in the development of flexible and stretchable wearable sensors based on nanomaterials and polymers, their bulky size prevents the sweat and air from the skin to pass through them freely and thus they are unsuitable for long-term continuous health monitoring [186]. In order to monitor health parameters accurately in a real-time manner with comfortability, truly wearable electronics applied in chronic disease care are required to be woven into fabrics to achieve high sensitivity, low power consumption and manufacturing costs as well as large-scale implementation [74]. In recent years, electronic textiles (E-textiles) as new wearable devices have attracted increasing attention in chronic disease care, because they can perfectly integrate the functional module with the soft and comfortable properties in the form of clothing. Consequently, the developments of textile-based wearable sensors with excellent responses to external stimulation from the human body are greatly desirable in chronic disease care. Textile-based/fiber-shaped wearable sensors offer the combined advantages of fiber and sensor compared with general flat and cubic wearable sensors supported by plastics or elastomers. These sensors have the merits of lightweight, flexible knitting, porous for permeability, excellent responses to mechanical deformation [26]. Therefore, textile-based or fiber-shaped wearable sensor is another essential research direction in the future.

C. New Trends in Applications

As reviewed in this article, the development of flexible and stretchable sensors has been largely driven by the various applications of wearable sensors. But this doesn’t mean the applications of these technologies are limited to the wearable sensors. Some of the new trends of such applications are discussed below. The application scenario of flexible and stretchable sensing technologies will be largely expanded.

1) From Wearable to Non-Wearable: As a visible trend in the wearable sensors applied in chronic disease care, more and more “non-wearable” sensors are demanded [242], [243]. The non-wearable sensing refers to the approaches of using the sensors which are not worn on the human body to accomplish the sensing functionality which is traditionally done by wearable sensors. For example, ECG signals can be captured by a bed mattress equipped with textile probes without the ECG probes being attached to the skin [244]. Better user experience, improved unobtrusiveness, and less interference by body movement are the motivations of non-wearable sensors. Many of the methods that are applied to improve the flexibility and stretchability of wearable sensors can also be applied to the non-wearable sensors, but new challenges are introduced. For example, the design of non-wearable sensors will not only consider the characteristics of the human body but also the characteristics of the “host object” i.e. the bed mattress in the above example.

2) From Human Body to Robot Body: One of the emerging research fields of robotics research is the Collaborative Robot (CoBot) [245], [246]. Unlike the traditional industrial robot which is usually “cold” and unsafe and thus has to be isolated by a fence during operation, the CoBot is “tender” and safe so that it can work side-by-side or hand-in-hand with a human without a fence. It is expected to be the key enabler of future robotized society where most of the boring and unskilled job will be done by robots especially service robots. To realize this dream, superior dexterity and guaranteed safety are the primary challenges to be addressed. Two important approaches have been applied concurrently to improve dexterity and safety: 1) covering the robot body by soft materials, 2) increasing the perception of the robot by the vast amount of sensors installed at “everywhere” of the robot body. One example is the ABB YuMi robot [152]. Obviously, the fundamental technologies originated from the flexible and stretchable wearable sensors will be important to build such a robot body of CoBot. Some emerging research has started in this direction (e.g., the robot hands with flexible and stretchable sensing “skin” covering all the fingers [247]). In this case, the sensors are used to sense the environment out of the “body”, which is opposite to the wearable sensors. The authors of this review believe, in the future, the body of CoBot will be more and more like the human body in terms of perception, dexterity, and safety. So, flexible and stretchable sensing technologies for robot body will become an important research field.

VII. CONCLUSIONS AND PERSPECTIVES

With the popularization of smart terminals, wearable systems have shown great market prospects and overwhelming needs of the chronic disease care. As the core component of wearable systems, the wearable sensor will play an important role in future function development. With the increased practical application requirements in chronic disease care, more new trends of wearable sensors are presented in this review, such as textile-based/fiber-shaped sensors, multifunctional sensors and self-powered sensors. For the biomedical application, flexible or stretchable features make the sensor conform to the skin or tissue well. However, sensor performance and reliability may be degraded when the sensor is under stretching and bending. In the future research of high-performance wearable sensors, significant effort should be made on such scientific issues as novel sensing principle, integration of multifunctional sensing, and technological breakthroughs in fabrication technology, material synthesis and device integration. Firstly, there is need for new materials and new signal conversion mechanism to enhance the performance and reliability of wearable sensor when being integrated with complex curved surfaces of human body. Secondly, low energy consumption and self-powered wearable sensors, battery miniaturization technology also need to be upgraded to achieve long-term sensing without frequently recharging. Thirdly, to ensure continuously wearable applications, long-term stability of the sensing performance and seamless attachment onto the body under cyclic multiaxial deformation should be improved. Researches on novel sensing mechanisms with the low cross-sensing phenomenon and efficient algorithms to decouple
the stimuli should be conducted. In addition, most of the reported wearable sensors with nano-based enhancement are relatively large or have a limited spatial resolution, which is a big challenge to realize miniaturized integration. Advanced manufacturing techniques in high resolution, high efficiency, and scalable patterning and integration techniques are in great need to improve the current wearable sensors. Developing these issues to improve sensing performance and flexibility of wearable sensors can facilitate their application in chronic disease care.

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hematological malignancies development and therapies that can intervene those processes or improve treatment status. Dr. Gu’s work could potentially lead to innovative treatment options for hematological malignancies, especially for lymphoma and leukemia. Recent publication: Cancer Cell 2017, Leukemia 2016, Blood 2012.

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