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Application of Microfluidics in Wearable Devices

Guo Chen, Jiangen Zheng, Liyu Liu, and Lei Xu**

Wearable devices integrated with various electronic modules, biological sensors, and chemical sensors have drawn large public attention. Due to their inherent advantages of superior stretchability, elaborate microstructure, high integration of multiple functions, and low cost, microfluidics are an excellent candidate and have already been widely used in wearable devices. Well-designed microfluidic devices can realize excellent multiple functions in wearable devices, including sample collecting, handling and storage, sample analysis, signal converting and amplification, mechanic sensing, and power supplying. Moreover, the microfluidic wearable devices with further integration of wireless modules have exhibited potential applications in healthcare monitoring, clinical assessment, and human and intelligent device interaction. This review focuses on the latest advances on multifunctional wearable devices based on microfluidics, primarily including general functions and designs of microfluidic wearable devices, and their specific applications in physiological signal monitoring, clinical diagnosis and therapeutics, and healthcare.

1. Introduction

With the development of modern technology, wearable devices become more common at daily life and work.[1–3] These wearable devices can realize real-time and effective monitoring of the physiological state of human body, which requires that these devices must be comfortable, stable, and compliant with human body especially the skin.[4–6] Tremendous research efforts have been dedicated to fabricate soft, skin-based, multifunctional wearable devices, and significant progresses have been made in recent years.[1,4,7–11] Commercial wearable products have been applied in physiological signal monitoring of human beings, and even in clinical diagnosis and therapeutics.[3,12–16]

Nowadays, microfluidics has been widely applied in wearable devices.[3,8] Microfluidics is a multidisciplinary technology for precise manipulation of minute amounts of fluids in a confined micro space,[17–19] which has been widely applied in various areas, including but not limited to organ on Chip,[20–24] drug delivery,[25–30] cell biology,[31–35] and electrochemical detection.[30,36–39] Microdroplets is another big category in microfluidics and offers a great number of opportunities in chemical and biological research,[40] such as chemistrode[41,42] and single cell/molecule assays.[43,44]

Microfluidics becomes excellent candidate of wearable devices for its inherent advantages.[45–48] First, microfluidics has good mechanical and adhesion properties. It is developed based on soft and stretchable materials, such as rubbers, acrylics, polydimethylsiloxane (PDMS), epoxies, silicones, cyanoacrylates, and hydrogels.[49,50] These materials are usually low modulus elastomers which deform easily under small pressures, minimizing slippage against the skin without detachment or facture.[51] Second, the micrometer size of channels and structures ensures the quick and high sensitivity of measurements,[52–54] on the other hand, the suitable size can miniaturize the wearable device without losing measurement accuracy.[55] Third, microfluidics has great functional versatility, since it can be easily integrated with electronic modules to realize multiple functions.[56,57] Fourth, the cost of microfluidic fabrication is relatively low, enabling the mass manufacturing.[58–60]

There are numerous excellent review papers on microfluidics and wearable devices. To name a few, Zhang et al.[61] introduced recent advances in microfluidics for cancer nanomedicine from fabrication to evaluation. Yetisen et al.[58] discussed consumer trends in wearable electronics, commercial and emerging devices, and fabrication methods. Chen et al.[62] focused on the achievements and challenges of mechano-based wearable healthcare. However, a review emphasizing on both wearable devices and microfluidics is still lacking. For instance, Gao et al.[63] focused on summarizing flexible electronics toward microfluidics-based wearable physical and chemical sensing. Wang et al.[3] discussed advances of the wearable biosensors for healthcare monitoring, and microfluidic sensor is only one example among many.

Therefore, the objective of this review is to comprehensively address the advantages, opportunities, and challenges of microfluidics-based wearable devices, and reveal that the microfluidics has become a rising star in the development of wearable devices. In this review, we will mainly focus on three subfields among the diverse achievements and advances in wearable devices based on microfluidics: Section 2 shows the general

Dr. G. Chen, J. Zheng, Prof. L. Liu
Chongqing Key Laboratory of Soft Condensed Matter Physics and Smart Materials
College of Physics
Chongqing University
Chongqing 400044, P. R. China
E-mail: wezer@cqu.edu.cn
Prof. L. Xu
Department of Physics
The Chinese University of Hong Kong
Kowloon 999077, Hong Kong
E-mail: xulei@phy.cuhk.edu.hk
The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/smtd.201900688.

DOI: 10.1002/smtd.201900688

functions and designs of microfluidics in wearable devices, including sample collection, handling and storage, sample analysis, signal transduction and amplification, mechanic sensing, and power supply. In Section 3, we will provide specific examples and review basic applications of microfluidics-based wearable devices in physiological signal monitoring, such as component analysis in sweat, interstitial fluid, and other biological fluids, skin temperature and hydration measurement, and bioelectrical analysis. We would also like to introduce the latest advances of multifunctional wearable devices based on microfluidics in areas of clinical diagnosis, therapeutics, and healthcare. In Section 4, we discuss some specific clinical and health care applications, such as drug storage and delivery, exercise assessment, and intelligent interaction between human and devices.

Guo Chen received his B.S. at the University of Science and Technology of China (2010), followed by a Ph.D. (supervised by Prof. Lei Xu) from the Chinese University of Hong Kong in 2014. He joined Chongqing University in 2014 where he has remained since. His research interests include soft condensed matter (experimental) and biophysics.

Lei Xu obtained his B.S. at the University of Science and Technology of China (2000), followed by a Ph.D. (2006) from Chicago University, and he worked as a postdoctoral fellow from 2006 to 2009 in Harvard University. In 2009, he joined the Chinese University of Hong Kong, and became professor in 2018. Lei's research interests focus on soft condensed matter experiments, including fluid mechanics, crystallization kinetics, colloidal glasses, active matter, drying, and cracking dynamics.

2. General Functions and Designs of Microfluidics in Wearable Sensors/Devices

In addition to the general advantages of wearable devices such as soft, elastic, and low cost, microfluidics can realize more functions by properly designing and fabricating specific structures, such as sample collection and storage, sample analysis, signal transduction and amplification, mechanic sensing, and power supplying.

2.1. Sample Collection, Handling, and Storage

In wearable devices for body fluid monitoring, samples, such as sweat, interstitial fluid, saliva, and tears, usually need to be collected and guided to reach reservoirs.[4,64] The smooth and efficient collection of samples is the first step in the successful operation of devices. Conventional body fluid collection often involves puncture of the skin,[65,66] or applying thermal heating, stress, or electric current across the skin,[67] and the sampling process need to be completed for multiple times at different time nodes with large amount of sampling volumes.[68] On microfluidic-based epidermal wearable devices, minimally invasive or even noninvasive sampling on demand is successfully realized, and because of the micro-scale of microfluidics, the sample volume can also be greatly reduced at each time.[45,69]

Microfluidic channels can obtain liquid samples using a combination of capillary force and action of the natural pressure (≈70 kPa) associated with perspiration.[45,70–75] Toonder et al.[70] designed and fabricated a sweat intake device by combining paper and a microfluidic channel in foil (**Figure 1**A). The paper absorbs sweat from skin surface when the device is attached to the skin, and then the microchannels and cavities in microfluidic foil will be filled with sweat by capillarity. Similarly, Rogers et al.[45] fabricated microchannel openings at a skin-compatible adhesive layer in their wearable microfluidic device to collect sweat samples.

Osmotic property is also an effective approach to collect liquid samples in microfluidic devices.[76] Velev et al.[76] integrated thin hydrogel disks with a microfluidic device. These disks were equilibrated in saline or glycerol and interfaced with a water-permeable membrane. An osmotic pressure difference across the membrane was created due to the high concentration of solute in the hydrogel, which drove fluid samples flow through the membrane and into the device (Figure 1B).

These sample collecting principles either by capillary effect or osmotic pressure are not only suitable for sweat, but also for tears and saliva.[77] These approaches can collect sweat or other biofluids once it is excreted to the outer skin surface, and they have no irritation on skin compared with the conventional pinprick sampling processes.

In addition to the capillary and osmotic collection of sweat, some other important methods, such as microdialysis[44,78,79] and microneedles,[80–82] also play key roles in the collection of interstitial fluids,[83] cerebrospinal fluid,[78,84] and blood samples,[85] have direct physiological and clinical relevance to many diseases and physical conditions. For example, Goud et al.[81] described an orthogonal electrochemical/biocatalytic hollow microneedle sensor array strategy to continuous minimally invasive monitoring of levodopa (L-Dopa) in the interstitial fluids.

Once collected, the liquid samples are transported to reservoirs or detection spots. Usually the captured liquid samples continuously wet the microfluidic channels to rapidly reach and fill the reservoir.[71] However, the samples need to be guided to designated chambers or fill a series of reservoirs sequentially in some cases. Microfluidics can also meet these requirements. For example, Rogers et al.[75] designed capillary bursting valves (CBVs) in their skin-mounted microfluidic devices to realize precise sampling capability. Each CBV is a microfluidic channel with a diverging section, and has its characteristic bursting

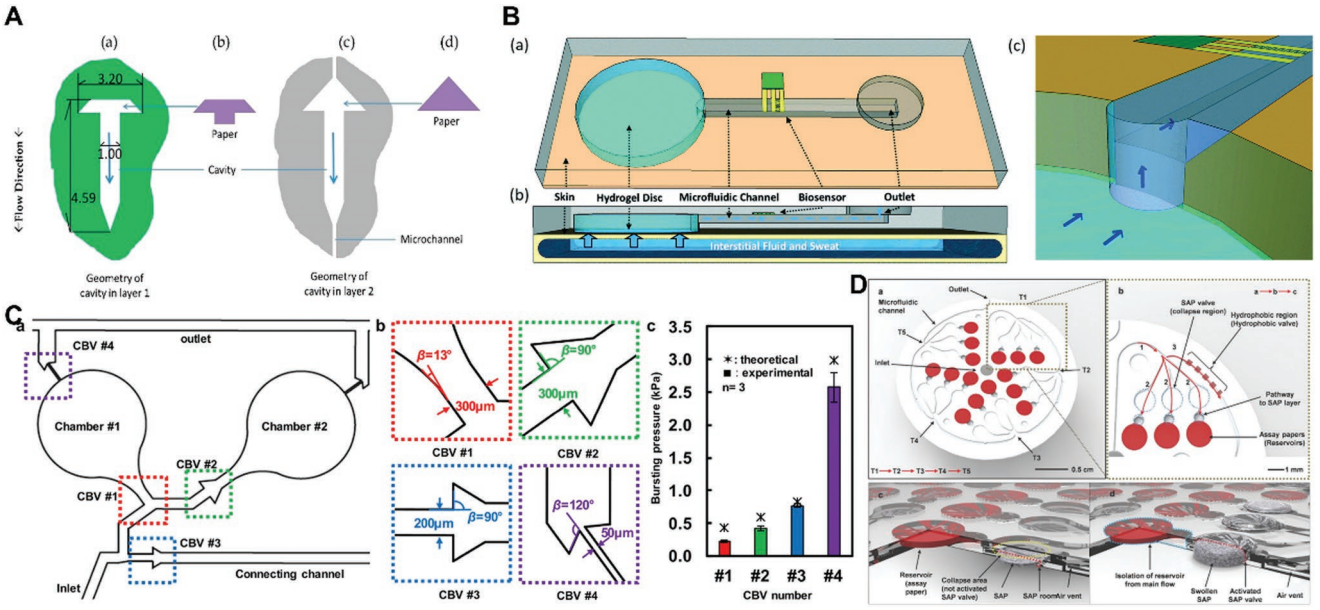

Figure 1. A) Designs of cavities in microfluidic foil. Reproduced with permission.[70] Copyright 2015, Elsevier. B) Schematic illustration of the device and osmotic driving process. Reproduced with permission.[76] Copyright 2017, The Royal Society of Chemistry. C) Schematic illustration of a unit cell in device and sketch of CBVs. Reproduced with permission.[75] Copyright 2019, American Chemical Society. D) Illustration of the epidermal microfluidic device with a detailed description of the reservoir and super absorbent polymer system. Reproduced with permission.[64] Copyright 2018, Wiley-VCH.

pressure (BP) by setting specific diverging angle, width, and height values of the channel (Figure 1C).[69,75,86] The liquid samples will first flow through the valve with lower BP and then reach other valves. Therefore, the samples can be guided to fill a collection of microreservoirs in a sequential manner. Another way to handle liquid samples in microfluidics is also introduced by the same team of Rogers.[64] They designed a collection of active valves based on superabsorbent polymer (SAP) materials in their chrono-sampling epidermal microfluidic device (Figure 1D). The SAP valve acts to close the inlet and outlet of each reservoir when the sweat reaches the valve by expansion due to hydration of the SAPs material, and can guide the sample flow from an inlet location into a collection of isolated reservoirs in a well-defined sequence, preventing contamination or mixing.

2.2. Sample Analysis

Microfluidics has a high degree of integration, and it could not only be used for collecting and storing samples, but also for sample analyzing. For this purpose, the microfluidic channels are usually integrated with electrodes, chemical sensors, or biosensors.[3,12,78] Recently, many chemical sensors and biosensing devices based on microfluidic channels have been developed for medical, environmental, and industrial applications.[87] Compared with the traditional instrument system, microfluidic sample detector has higher sensitivity and signal-to-noise ratio, as well as a faster response speed.

For example, colorimetric sensing is a common and intuitive sample analysis method in wearable microfluidic devices, and it provides a simple and rapid visual readout of sample type and concentration for further digital analysis.[45,55,64,75,88] In colorimetric strategy, chemical analyses or fluorescent probes are usually pre-filled in the microreservoirs. For example, Rogers et al.[45] embedded different chemical analyses in the orbicular serpentine channel to serve as colorimetric indicators. Once in contact with the sweat samples, these chemical analyses respond in colorimetric manner to the marker's ingredients, such as chloride and hydronium ions, glucose, and lactate. Quantitative colorimetric analysis conducted by UV-vis spectroscopy and optical images can further provide detailed concentration data of corresponding analyte (**Figure 2**A).

Counting analysis on cells or particles can also be realized in wearable microfluidic devices.[89,90] Javanmard et al.[91] combined parallel electrodes of the sensor with microfluidic channels in their wearable microfluidic impedance cytometer (Figure 2B). These electrodes were connected with microcontroller and soldered to circuit's terminals. When a particle flows through the electric field between two parallel electrodes within a microfluidic channel, a variable impedance is induced and amplified to output a voltage signal. The signals are then transmitted to the smartphone by a Bluetooth module, and then are converted into cell counts.

Besides particle counting, the electrical impedance method can also be applied to measure sample conductivity and rate in real-time.[54,92] Roger et al.[92] integrated gold-coated copper electrodes with microfluidic structure (Figure 2C). The electrodes have well-defined spacing. When the microchannel is filled with samples (such as sweat), the resistance between electrodes changes and sample conductivity can be obtained.

In addition, some sophisticated sample analysis, such as real-time quantitative monitoring of biomolecules, requires to incorporate complementary metal-oxide-semiconductor (CMOS) circuitry inside the microfluidics channels for integrating various sensors and signal processors for cell manipulation and detection.[93–96] The high density arrays of recording/stimulating

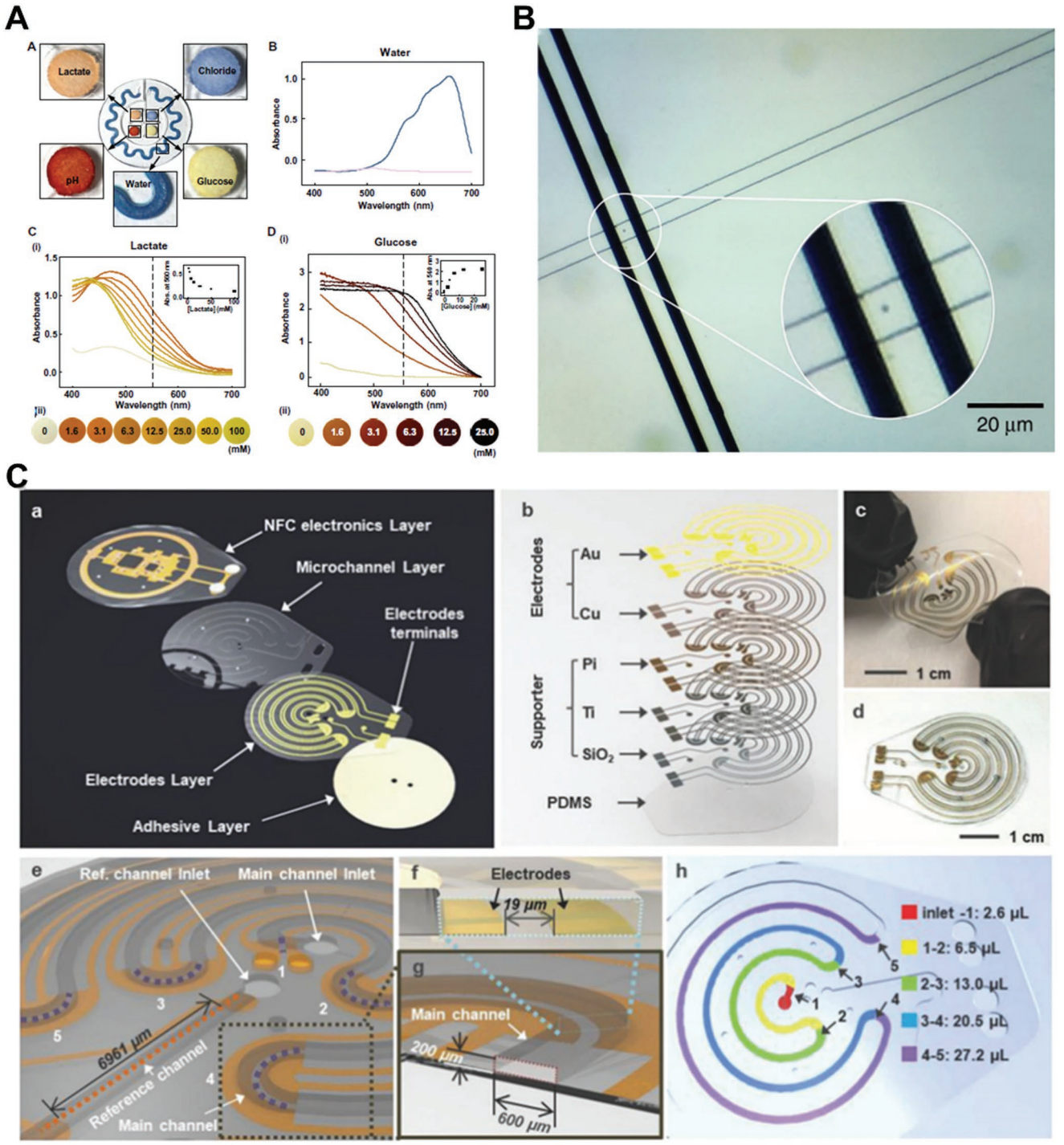

Figure 2. A) Quantitative colorimetric analysis of markers in sweat. Reproduced with permission.[45] Copyright 2016, American Association for the Advancement of Science (AAAS). B) Electrodes in microfluidic impedance cytometer. Reproduced with permission.[91] Copyright 2018, The Author(s). Published by Springer Nature. C) Schematic illustration and pictures of wireless microfluidic system with capabilities in digital measurements of sweat. Reproduced with permission.[92] Copyright 2018, Wiley-VCH.

electrodes available on CMOS chip allow the active monitoring of individual cells within a cellular network. For example, Kim and Yoon[94] presented a label-free CMOS field-effect transistor sensing array to detect the surface potential change affected by the negative charge in DNA molecules.

2.3. Signal Transduction and Amplification

An inherent advantage of microfluidics is its small size. The delicate structures of microchannel help to reduce sample volume, and further realize amplifying and measuring of tiny signals

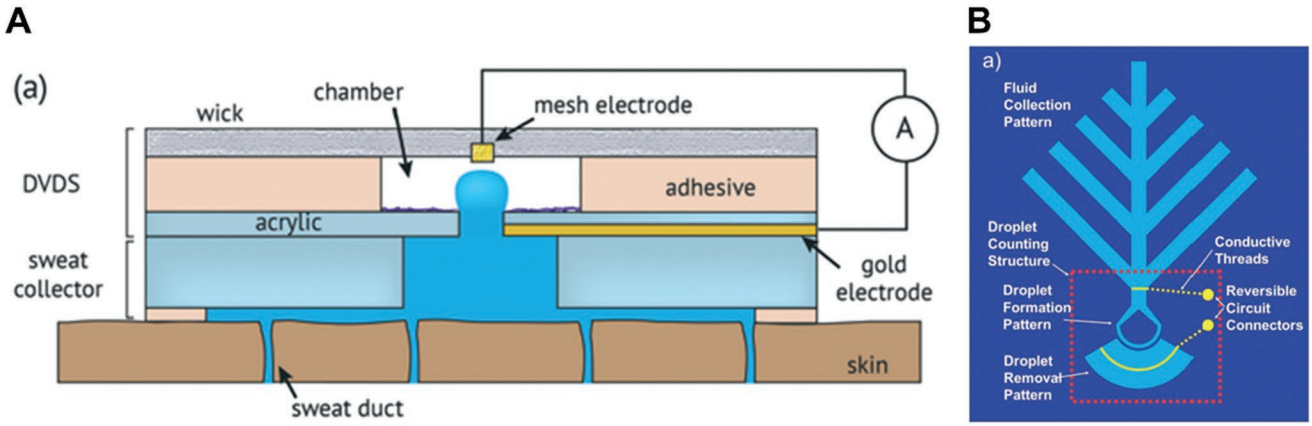

Figure 3. A) Schematic illustration of digital volume dispensing microfluidic system. Reproduced with permission.[54] Copyright 2019, The Royal Society of Chemistry. B) Schematic illustration of wearable digital droplet flowmetry. Reproduced with permission.[97] Copyright 2017, The Royal Society of Chemistry.

combined with sensitive electrical strategies.[54,97] For example. Gomez et al.[54] developed a microfluidic flow rate sensor by embedding two electrodes in microchannel (**Figure 3**A). Their device was demonstrated to be able to measure flow rate as low as 25 nL min^{-1}. Once the liquid sample forms a capillary bridge between two electrodes, the circuit is connected and a current is generated and recorded. Then a strong wicking event occurs and breaks the capillary bridge and resets the process. The weak flow rate signal is converted and amplified into significant electric signal using this method.

Pan's team[97] proposed a digital droplet flowmetry, which integrates a microfluidic network with a digital counting/measurement circuitry using a resistive measurement principle (Figure 3B). The measurement principle is similar to Gomez's device. The collected liquid samples are transported to a microfluidic junction to form a drop. When the drop growths to reach an identical volume, it breaks the superhydrophobic gap, leading to a decrease of resistance of circuit. As a result, the slow and continuous flow information is converted into discrete drop volume, from which the flow rate can be assessed by the digital counting circuit.

2.4. Mechanic Sensing

The conversion of tiny strain changes into a macroscopic measurable quantity is always a big challenge in mechanic sensing. The liquid-based microfluidic tactile sensing devices offer a suitable avenue for high sensitivity detection. Conventional liquid-based microfluidic strain sensors assemble working liquid inside microchannel. An external load or a strain leads to the displacement of the working liquid in the microfluidic channel, which changes the capacitance or resistance of the device depending on the type of working liquid.[98] Graphene and similar 2D-material suspensions become primary candidates for working liquids due to their excellent electrical properties and superior mechanical flexibility.[98] For example, Lim et al.[98] utilized graphene oxide nanosuspension as working liquid in the liquid-based microfluidic tactile sensor to measure corresponding resistance change (**Figure 4**A). Their device is able to differentiate subtle hand muscle-induced motions.

Liquid metal alloy is another choice for microfluidic pressure sensor. Javey's team[52] introduced a microfluidic tactile diaphragm pressure sensor based on embedded Galinstan microchannels (Figure 4B), realizing resolution of sub-50 Pa changes in pressure with sub-100 Pa detection limits. Dong et al.[99] combined piezoresistive graphene and microfluidic liquid metal to fabricate flexible strain sensor, and their sensor is capable of detecting the angular motion of a human wrist.

Although conventional liquid-based microfluidic sensors have superior sensitivity, the fabrication process is complex and material selection is limited. Moreover, their mechanical deformability is usually restricted and thus they can rarely achieve high strain and recovery ability. To address this issue, Hou's group[53] developed a universal strategy to build bioinspired flexible microchannel system based on elastomer in which potassium chloride ionic solution is the working liquid (Figure 4C). Resistance change of microchannel was measured under different tensions. Their elastomer-based microchannel exhibits excellent high strain (967%) and recovery ability.

These common microfluidic physical sensors rely on the detection of electrical resistance, inductance or capacitance change due to mechanical deformation. Therefore, an external circuit is always required to transmit the electronic signals. Thus, they are not practical for some applications such as strain sensing in eyes. Recently, transparent, biocompatibility, and flexibility microfluidic sensors with a passive visual readout have aroused wide interest in wearable applications.[100]

Araci et al.[100] reported a passive integrated microfluidic strain sensor with a detection limit of <0.06% for uniaxial and <0.004% for biaxial strain, and applied it to pressure monitoring in porcine eyes by embedding the sensor in silicone contact lenses. Their sensor consists of a liquid reservoir, a sensing channel, and an air reservoir, which are connected in tandem (Figure 4D). The axial stretching or releasing will change the volume of microfluidic liquid chamber and leads to a vacuum effect. A displacement of the air–liquid interface is produced under the pull of vacuum and can be detected with a smartphone camera.

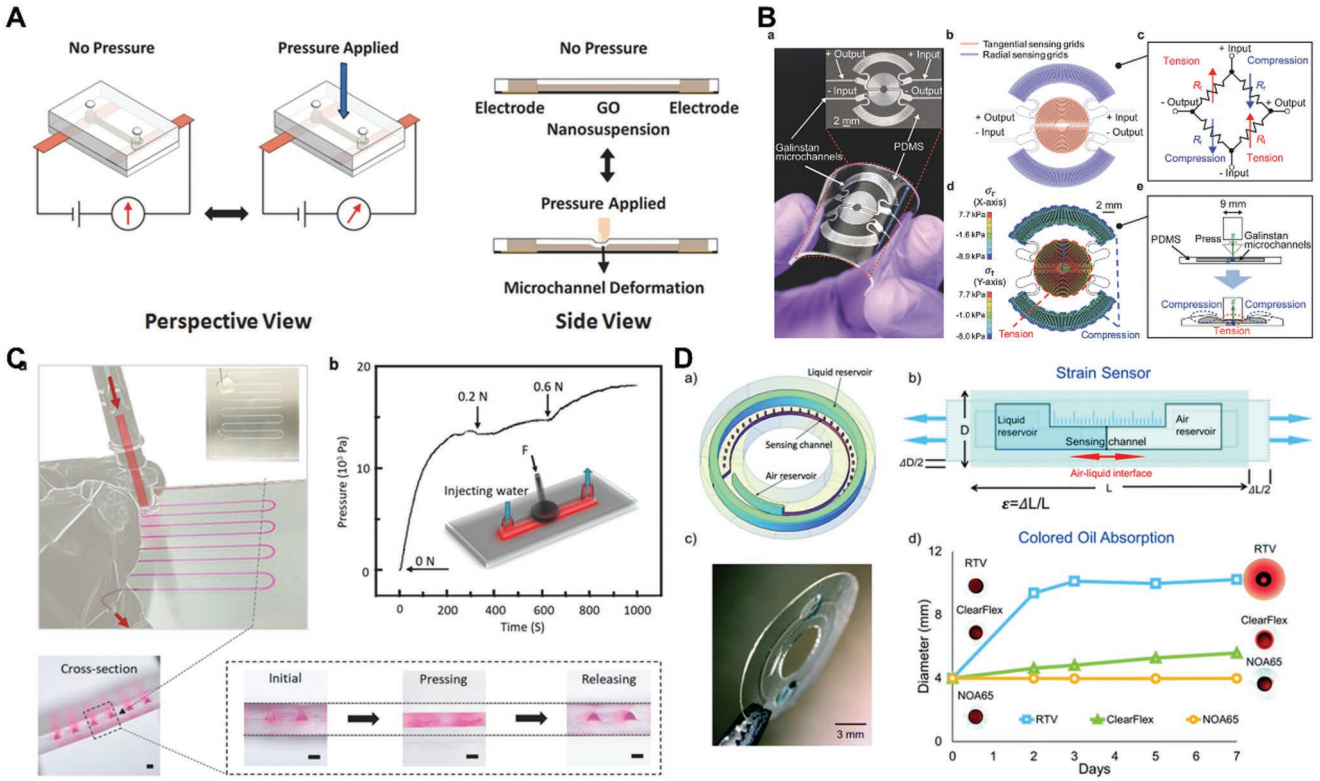

Figure 4. A) Working mechanism of tactile sensing device. Reproduced with permission.[98] Copyright 2016, Wiley-VCH. B) Microfluidic tactile diaphragm pressure sensor. Reproduced with permission.[52] Copyright 2017, Wiley-VCH. C) The elastomer-based microfluidic pressure sensor. Reproduced with permission.[53] Copyright 2018, Wiley-VCH. D) Schematic illustration of the configuration of microfluidic strain sensor. Reproduced with permission.[100] Copyright 2018, The Royal Society of Chemistry.

2.5. Power Supply

Wearable electronics have gradually become an indispensable part of life in recent years due to their remarkable applications. One major challenge is how to supply powers to these wearable electronics with lightweight and portable energy-storage devices.[101] Conventional button cell is not always a perfect choice because it has poor flexibility and is not suitable for some particular circumstances, such as underwater. Therefore, various flexible energy-storage devices, such as fiber-shaped micro-supercapacitors, have attracted enormous interests because of their high flexibility and weavability.[101] However, their energy density and charging capability are usually quite low, due to the low effective specific surface area and nonuniform or less pore distribution. As a result, they cannot compete with traditional batteries in practical applications.

Although these issues cannot be addressed by microfluidic channels only, microfluidic-oriented strategy, such as microfluidic-spinning technique, may provide a possible solution.[101–104] Chen's group[101] proposed a microfluidic-directed method to synthesize inhomogenous fibers with large specific surface area and uniform porous structure (**Figure 5**A). Their supercapacitor displays significant improvements in electrochemical performance and has been integrated into flexible and fabric substrates to successfully power various electronics.[102]

Yu's team[105] developed another low-cost and easy-to-manipulate pencil-drawing method to produce controllable power device based on paper microfluidics and a wax printing process (Figure 5B). Their approach overcomes the key technical challenge of bidirectional control of current and is able to drive electropolymerization, and electrochemiluminescence system.

3. Physiological Signal Monitoring of Microfluidics-Based Wearable Devices

The above section has introduced the general functions and general designs of microfluidics in wearable devices. It is precisely because of such superior functional merits that microfluidic wearable devices are practically applied in many aspects of daily life, including but not limited to physiological signal monitoring, healthcare products, clinical diagnosis, and therapeutics. In the following sections (Sections 3.1.–3.5.), we would mainly review the current applications of microfluidic wearable devices in the specific field of physiological signal monitoring.

3.1. Component Analysis of Sweat and Interstitial Fluid

In wearable sensing, sweat is one of the most straightforward targets since it is easy to acquire, and can be obtained continuously.[70] Sweat is an epidermal available biofluid with varied salinity (10×10^{-3}–100×10^{-3} M) and pH (4.5–7.0), and it is excreted from sweat glands, which are distributed throughout

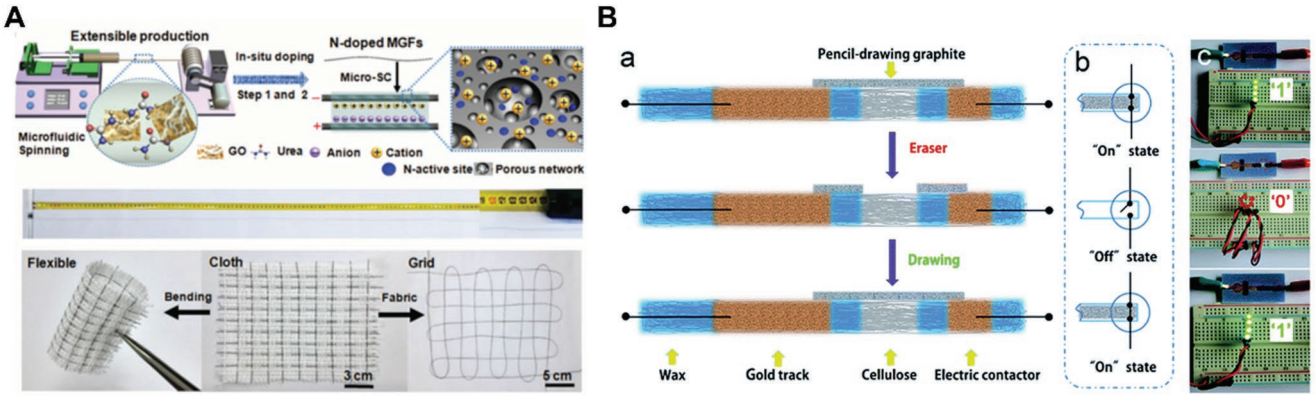

Figure 5. A) Microfluidic-directed technique for creating uniform graphene fibers. Reproduced with permission.[101] Copyright 2017, Wiley-VCH. B) Fabrication and operation of paper microfluidic bidirectional circuit switch platform. Reproduced with permission.[105] Copyright 2018, The Royal Society of Chemistry.

the human body at a density of 10 to 100 sweat glands per square centimeter on skin.[7] Sweat contains a variety of components, including glucose, electrolytes, lactate, hormones, enzymes, and proteins.[4,92] Some of them are natural biomarkers reflecting health status of wearer. For example, sweat chloride concentration is a widely accepted diagnostic screening tool for cystic fibrosis disease.[64] Not only the concentrations of glucose, lactate, and electrolytes (including but not limited to chloridion, sodion, potassium ion, zinc ion, hydrion) are important, but also the sweat rate and sweat loss

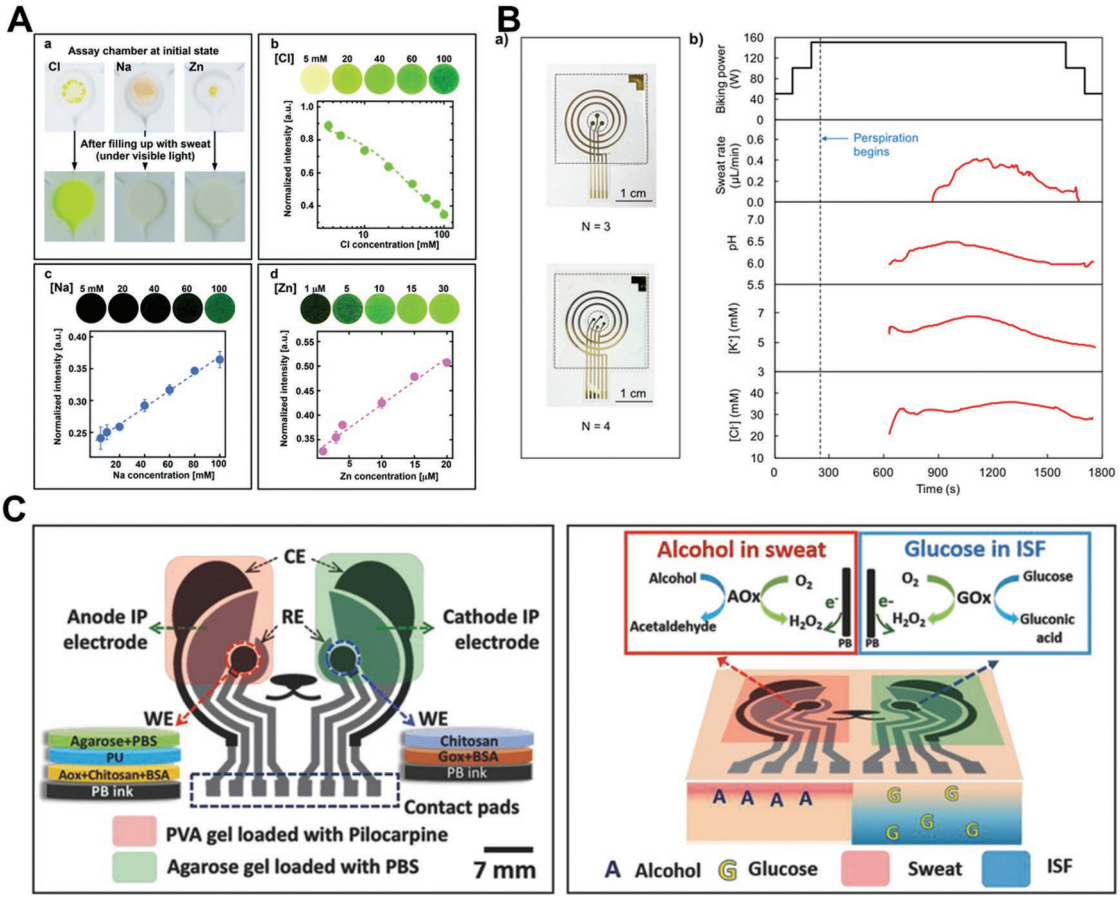

Figure 6. A) Fluorescence images of chloride, zinc, and sodium assays and the dependence of the fluorescence intensity on concentration. Reproduced with permission.[88] Copyright 2018, The Royal Society of Chemistry. B) Optical images of microfluidic sweat patch and sweat compositions measurements. Reproduced with permission.[72] Copyright 2018, American Chemical Society. C) Schematic illustration and operation principle of microfluidic device for simultaneous noninvasive sampling and monitoring of sweat and interstitial fluid. Reproduced with permission.[4] Copyright 2018, The Author(s). Published by Wiley-VCH.

can provide useful information about psychophysiological status. For instance, excessive loss of sodium and potassium in sweat could result in hyponatremia, hypokalemia, muscle cramps, or dehydration.[106] In addition, sweat regulates body temperature dynamically in response to environmental factors and physiological conditions, and insufficient sweating can lead to life-threatening heat stroke, a leading cause of death in young athletes.[64,107]

In wearable sweat monitoring devices, there are two key challenges: 1) minimally invasive or noninvasive of sweat sampling in different situations such as aquatic or arid environments,[108] and 2) quantitative and rapid analysis of many parameters in real-time. The first challenge may be relatively easy to address by microfluidics because of its superior noninvasive ability as discussed in Section 2. Rogers' team[108] made a waterproof epidermal microfluidic device for sweat analysis by sealing the microfluidic system with an elastomer (poly(styrene-isoprene-styrene)). The excellent mechanical properties of elastomer improve the stretching, bending, and twisting ability of device, and their device can even work well while fully underwater for hours.

Moreover, microfluidic-based wearable sensing devices have also exhibited potential advantages to address the second challenge.[88] For example, Roger's group[92] introduced a soft and skin-compatible microfluidic device for digital monitoring of sweat. Their device can quantify sweat conductivity and rate in real-time and the data can be wirelessly transmitted to electronic devices with near field communications technique. Another fluorometric skin-mounted microfluidic device developed by them[88] enables quantitative, rapid analysis on concentrations of target analytes in sweat, including chloride, sodium, and zinc, with accuracy that matches that of conventional laboratory techniques (**Figure 6**A). Wang group's epidermal microfluidic electrochemical detection platform[71] achieved rapid filling of detection reservoir within 8 min by optimization of sampling process and microchannel layout. Their device can biosense lactate and glucose levels in sweat using the corresponding immobilized oxidase enzymes as reactant in microreservoirs. Javey et al.[72] developed a spiral-patterned microfluidic sensor and they demonstrated that the device can be used for dynamic sweat secretion analysis on sweat rate and the concentration of sweat constituents, such as pH, Na^+, K^+, Cl^-, by simultaneously incorporating more sensing electrodes in the collection reservoir (Figure 6B). Similarly, some other groups[7,57,64,70,73,109] also reported their multiparameter microfluidic wearable sweat analyzers to real-time and continuous monitoring of sweat compositions.

Besides sweat, interstitial fluid is another biofluid that usually locates under the skin surface and fills the interstitial space. But it can be readily and noninvasively accessed from skin surface by iontophoresis or sonophoresis (ultrasound).[110,111] Moreover, the composition of interstitial fluid is very similar to that of blood in terms of salt, protein, glucose, and ethanol contents, since they can diffuse through the endothelium of blood vessels.[4,112,113] Therefore, some biomarkers in interstitial fluid can reflect the physiological statue of blood. For example, the glucose level in interstitial fluid is closely related to the blood glucose concentration and can help to reflect the healthy states of diabetic patients.[14] A few works have focused on monitoring H_2O_2, pH, lactate, glucose, and ethanol in interstitial fluid either in minimally invasive or noninvasive devices.[114–118]

Dual sampling and analysis of interstitial fluid and sweat in real-time would provide more comprehensive information about health status of human. However, it is difficult to achieve in one wearable platform since the two biofluids share the same sampling sites at the skin surface and the mixing seems to be unavoidable.[4] Wang et al.[4] introduced an approach to simultaneously and noninvasively sample and analyze two different biofluids with a single wearable device: they have successfully realized the concept in experiment through the parallel operation of reverse iontophoretic interstitial fluid extraction and iontophoretic delivery of sweat at separate locations of the same platform (Figure 6C). Their system allows simultaneous sampling of interstitial fluid and sweat at two physically separate locations that have different electrochemical biosensors for monitoring the corresponding biomarkers. However, this approach also has drawbacks since it can only analyze alcohol in sweat and glucose in interstitial fluid, and much endeavor is required for further development.

There are also some worries about the lifetime of microfluidic in wearable devices due to the possible clogging, which may shorten the lifetime of devices and is a major obstacle that microfluidic channels are facing. Some strategies have been proposed to solve this problem, e.g., Mossige et al.[119] achieved clog-free concentration and separation of complex algal cells by exploiting hydrodynamic interactions around trilobite-shaped filtration units in their microchannels. Furthermore, lots of microfluidics-based wearable devices, such as sweat monitoring sensor, are disposable.[120] In addition, due to its excellent sealing, the device can be used for hours even in some extreme conditions,[108] which ensures that there is enough time to complete corresponding monitoring. Thus, lifetime is usually not a big problem.

3.2. Component Analysis for Other Biological Fluids

In addition to sweat and interstitial fluid, other biological fluids, including tears, saliva, and blood, are also useful samples for clinic diagnostic measurement, because they contain many biomarkers to reflect physiological status of human. Microfluidic wearable devices developed in the last decade exhibit superior properties in these biological fluids sensing as well.

Tears, along with sweat and saliva, is a main biofluid that contains multiple physiologically relevant chemical constituents that can be easily monitored in a continuous noninvasive real-time fashion. In particular, the diabetes mellitus can affect the production of tears, their composition, and environment.[121] For example, the glucose concentration in tears is correlated with that in blood to some extent, thus most wearable microfluidic biosensors for tear analysis are applied in diabetes monitoring by the determination of glucose in tears using some suitable contact lens.[12,114,122] For example, Chu et al.[77] have demonstrated the monitoring of tear glucose in situ on rabbit eyes with a contact lens biosensor incorporating microfluidics and glucose analysis (**Figure 7**A). But there are still limitations that need to be overcome before its clinical application such as the specific correlation of tear glucose with blood glucose,[12]

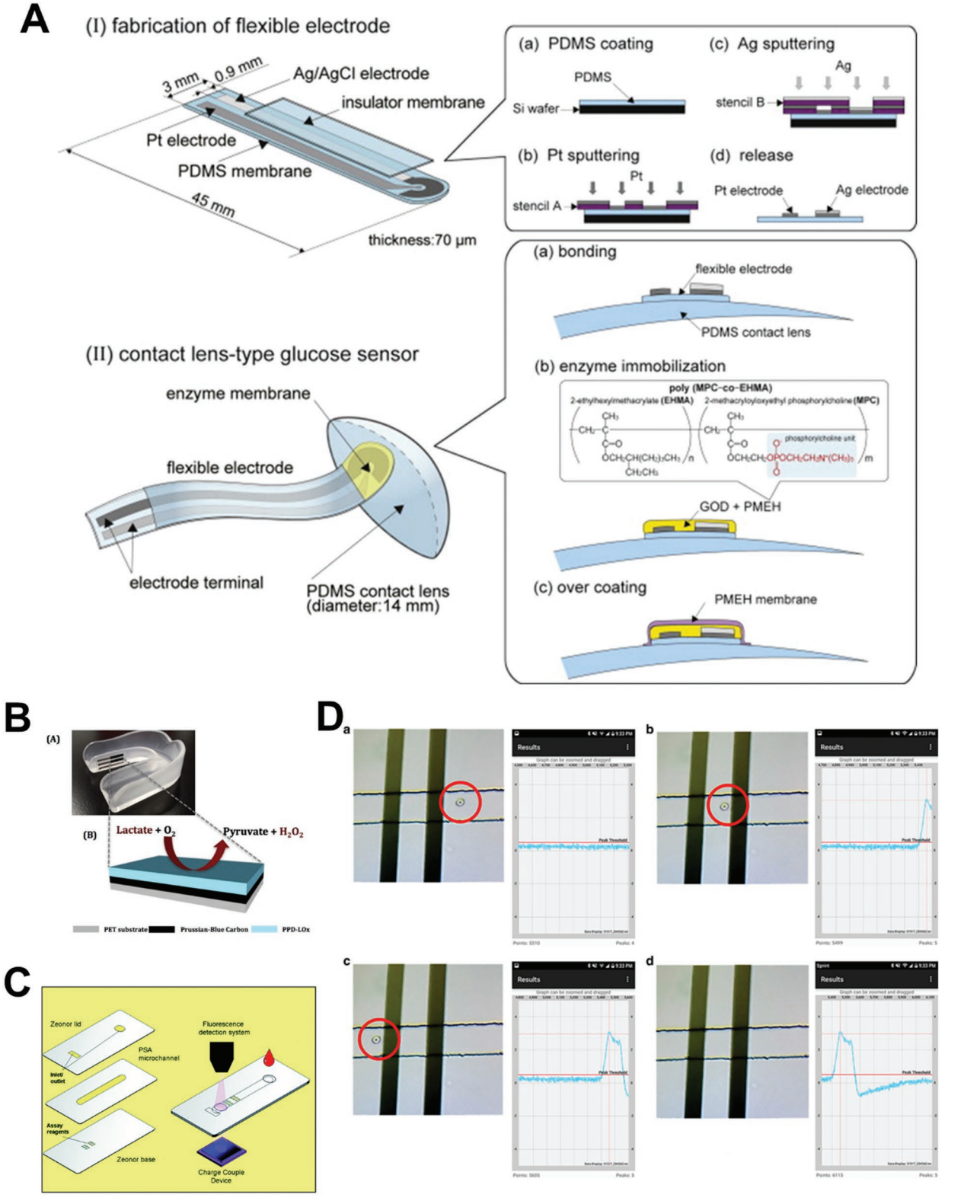

Figure 7. A) Fabrication method of the contact lens-type glucose biosensor. Reproduced with permission.[77] Copyright 2011, Elsevier. B) Photograph of the mouthguard biosensor for salivary lactate monitoring. Reproduced with permission.[127] Copyright 2014, The Royal Society of Chemistry. C) Schematic of the microfluidic chip for anticoagulants monitoring. Reproduced with permission.[129] Copyright 2016, The Royal Society of Chemistry. D) Images illustrating the cytometry device for human red blood cell counting with online smartphone readout. Reproduced with permission.[91] Copyright 2018, The Author(s). Published by Springer Nature.

and the insufficient analysis of glucose in diabetes monitoring. It is known that diabetes can affect the production, composition of tears, and the anterior ocular environment. Future endeavors are needed to develop microfluidic tear sensors for monitoring glucose and other important analytes.

Saliva is another readily available and valuable source of biofluids accessible in a noninvasive fashion. The sensing of saliva is beneficial to detect the presence of drugs, and monitoring healthy conditions of mouth.[123–125] The research of saliva sensing is mainly focused on the measurement of bacteria, cortisol, phosphate, amylase, glucose, and lactate. For example, the inorganic phosphate concentration is an important index in clinical analysis, and the amount of phosphate in saliva is three orders of magnitude more than blood serum.[126] In another example, Wang et al. proposed a full integration of a mouth guard platform (Figure 7B) to monitor lactate levels over the physiological range 0.1×10^{-3}–0.5×10^{-3} m. But their system evaluation was restricted to bench measurements and cannot realize real-time sensing in-mouth.[127]

Blood is by far the most understood sample for diagnostic measurements. For instance, the plasma concentration of human leucocyte elastase is always related with inflammatory bowel disease.[128] The constituent chemical analysis of blood usually involves invasive sampling.[12] In blood sensing, the common detected bioinformation contains glucose, anticoagulants, cancer cells, and other pathological markers. For example, monitoring the anticoagulant level in blood can help to prevent coagulation disorders. Killard et al.[129] presented a novel microfluidic device for monitoring the effect of two anticoagulants, unfractionated heparin, and low molecular weight heparin using fluorescence detection (Figure 7C).

Besides constituent analysis, microfluidic devices can also quantify cell numbers or flow rate noninvasively. A well-known example is the low or high levels of red blood cell, white blood cell, or platelet can provide significant insight into a patient's health.[130–132] However, a complete blood counting test is usually based on invasive sampling, such as skin prick. Moreover, such tests can only be performed by a professional staff using expensive and bulky equipment primarily located in the laboratory. Although fluorescence-based cytometers seem to be a possible choice, it requires a tedious labeling procedure of biological cells with fluorophores.[91,133,134] Wearable microfluidic impedance cytometry device invented by Javanmard group[91] is a proper solution for this task. Their portable and fully integrated system is implemented on a flexible circuit wristband with on-line smartphone readout for cell counting and analysis (Figure 7D). Microfluidics can also deal with cell manipulation in blood, e.g., Hammond group[135] developed a strategy to capture and release circulating tumor cells from the blood of breast cancer patients using a microfluidic approach.

3.3. Temperature Monitoring

Skin temperature is an important physiological indicator,[136] which is associated with cardiovascular health, cognitive state, body lesions, and tumor malignancy.[137] Clinical medicine sometimes requires long-term real-time monitoring of temperature for particular groups, such as new-born babies or patients under anesthesia.[56] Traditional contacting temperature measurement technique, such as mercury thermometer, is not suitable or convenient for babies. The newly emerged noncontacting infrared thermometers is difficult to achieve focused temperature monitoring in local area and is unstable in measurement accuracy since it is vulnerable to environmental influences.

The flexible wearable microfluidic temperature equipment provides a good solution for this challenge, and many epidermal temperature sensors have already been developed, which become more and more important in temperature-related disease diagnosis and human healthcare.[138,139] For example, Rogers group incorporated a colorimetric temperature sensor in their skin-integrated multifunctional microfluidic device.[75] The temperature sensor is a ternary cholesteric liquid crystalline mixture of cholesteryl oleyl carbonate, cholesteryl nonanoate, and cholesteryl 2,4-dichlorobenzoate, encapsulated by a film of polyester with black background. The sensor exhibits different colors at varied temperatures and enables colorimetric determination of temperature across a range from 31 to 37 °C. For instance, it is red at 32 °C, green at 33 °C, and blue at 34 °C. The temperature of sweat is determined immediately as it emerges from the skin and reaches the sensor, and the influence of environment can be ignored. Their system is able to measure the temperature of sweat, which reflects the skin temperature, with the uncertainties of 0.2 °C in a real-time manner (**Figure 8**A). Another epidermal microfluidic device proposed by them[108] also realized precise skin temperature measurement and has been demonstrated to be effective even in extreme situations, such as underwater.

3.4. Skin Hydration

The water content of the skin, especially the stratum corneum, is responsible for keeping the skin smooth and soft.[140] Improper skin hydration can lead to eczema, atopic dermatitis and accelerates the aging of skin, thus precise and quantitative monitoring of skin hydration is useful in preventing skin-based pathologies, and regulating external appearance.[137,141–143] For athletes, hydration status is a key indicator since fluid deficiency impairs their endurance performance and increase carbohydrate reliance.[57] For workers in extreme conditions, severe dehydrate may cause death.[144]

Some commercially available noninvasive methods, such as optical spectroscopic techniques, Raman spectroscopy, magnetic resonance spectroscopy, indirect approaches including evaluation of mechanical properties of skin or its surface geometry, have been proposed to characterize skin hydration levels.[145–150] Each device offers a unique possibility of studying a specific phenomenon in intact skin that may correlate to skin hydration level. But the most reliable and established skin hydration measurement is based on impedance monitoring since the skin hydration level is reflected by electronic or thermal parameters,[56,140,141] such as thermal conductivity, thermal diffusivity, volumetric heat capacity and electrical impedance (Figure 8B). The measurement principle is to correlate the electrical or thermal parameters of biological tissues to their water content, and a plenty of devices have already been developed based on

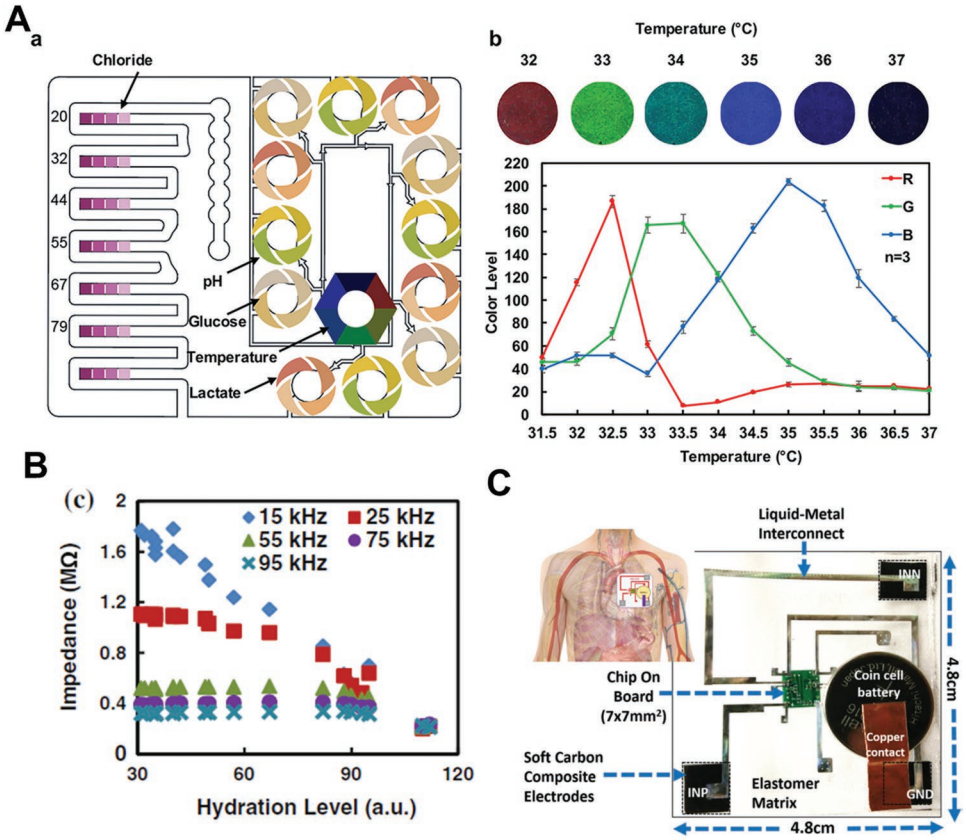

Figure 8. A) Optical images of the color development of a thermochromic liquid crystal temperature sensor as a function to temperature. Reproduced with permission.[75] Copyright 2019, American Chemical Society. B) Hydration level-dependent impedance amplitude at selected measurement frequencies. Reproduced with permission.[141] Copyright 2012, The Author(s). Published by AVS. C) ECG patch based on microfluidic elastomer matrix. Reproduced with permission.[161] Copyright 2018, Wiley-VCH.

this conception.[56,141,143,144,151] For example, an embedded piezoresistive microcantilever sensor has been proposed to provide the appropriate hydration level in the human body.[152,153]

To replace the expensive, bulky instruments and achieve low-cost, long-term hydration monitoring, ultrathin and stretchable electronic wearable hydration sensors have been proposed and developed.[57,144] For example, Yokus and Daniele[154] designed and fabricated a capacitance hydration sensor with serpentine-interdigitated electrodes via photolithography techniques and integrated it with soft textile-based system to monitor skin hydration level. Zhu et al.[144] synthesized silver nanowires inlaid in a PDMS matric to build up a flexible hydration sensor. Their compliant, stretchable electrode provides a conformal electrical and mechanical interface to the skin and can be worn continuously to monitor the skin hydration based on the skin impedance method.

3.5. Bioelectrical Signals

Bioelectrical signals have been widely used for monitoring human activities and clinical diagnoses. The common bioelectricity measurements associated with human body incorporate electrocardiogram (ECG), electroencephalogram (EEG), electromyogram (EMG), and electrooculogram (EOG). Among them, ECG is a quite popular bioelectrical analysis method in clinic for cardiac diseases and for assessing the physiological fitness of athletes.[56,155] For example, ECG can help to diagnose heart arrhythmias,[156] and when abnormal heart rhythms or heart failure is detected, timely and accurate treatment is vital.[51]

Sensing of electrophysiological signals involves measurements of electrical coupling between biological tissues and electrodes. Those electrodes are usually encapsulated by a dielectric layer to facilitate sterilization and enable cleaning for reuse. Such protection also enhances safety by eliminating leakage currents and electrical shorts between devices and the human body.[157] The electrode–skin interface impedance and noise induced by motion can largely determine the quality of an ECG measured with surface electrodes.[13,51] Conventionally used wet electrodes for surface ECG recording are unfavored owing to their skin irritating and drying nature. Although rigid dry electrodes are long-term wearable and reusable, they suffer from a large electrode–skin impedance and motion artifacts. Therefore, soft stretchable electrodes have the obvious advantage of minimizing slippage against the skin by being able to deform with the skin without detachment or fracture.[51] Nowadays, a variety of small and convenient wearable devices based on extremely thin, soft, and dry electrodes has been developed by integrating inorganic or organic conductive materials with elastomeric frameworks.[158,159] These conductive materials include but not

limited to gold, silver, copper, carbon nanotube, graphene, and liquid-metal.[51,158–160] For example, Thean's team[161] reported a novel integration of a wearable and stretchable ECG patch (Figure 8C), and their patch was monolithically integrated with low-resistance sensor electrodes and liquid-metal microfluidic interconnections in an elastomer matrix. The elastomer materials provide sufficient pliability to enable conformal contact to the human chest. Their microfluidic ECG patch is able to realize low-noise signal acquisition that is comparable to commercial wet electrodes approach.

In additional to ECG analysis, EEG, EMG, and EOG also play key roles in health monitoring and have been realized in wearable devices based on microchannels.[5,162–165]

4. Clinical Diagnosis/Therapeutics and Healthcare

Microfluidic wearable devices have exhibit their great practical applications in physiological signals monitoring. Moreover, with the increasing demand for a healthy life, simple-to-use, point-of-care, and noninvasive wearable devices allowing medical self-testing at home have enormous potential values.[114,166–170] Microfluidics has and will continue to play an important role in these areas. In the following sections (Sections 4.1.–4.3.), we would mainly review the recent developments of microfluidic wearable devices toward clinical applications and healthcare.

4.1. Drug Storage/Delivery

One of the key challenges in the treatment of disease is the delivery of drugs to some specific locations with controlled dosing and on demand. For example, auditory disorders are common diseases of the elderly,[171,172] but the drug delivery in the inner ear is relatively inaccessible both pharmacologically and anatomically, due to the cochlear barrier and the delicate anatomic structure of cochlea.[173,174] Some attempts have been tried to deliver the drug into middle ear and onto the round window membrane to intensify therapeutic efficacy,[173,175] however these delivery methods depend on passively diffusing of drugs, which is slow and unpredictable. Similar situation happens for the treatment of eye diseases, such as dry eye, cataract, and glaucoma.[100,176,177] The traditional eyedrop delivery in eye relies on manual dripping, which is imprecise and uncomfortable. To improve this situation, portable wearable devices for drug delivery based on microfluidics have been proposed and developed.[178]

For example, Borenstein's team[173] developed a micropump and a drug reservoir integrated in an implantable and wearable delivery system for controlled, automated inner-ear drug delivery (**Figure 9**A). Their device showed on-demand dosing capability by using a glutamate receptor antagonist as a physiological indicator of drug delivery. They have demonstrated the high efficiency and ability of long-term usage of the device in guinea pig experiments. Another work reported by Araci et al.[100] is not directly related to drug delivery, but it may contribute to the assessment of proper dosing time for some particular diseases involving pressure change of tissues, such as glaucoma. High intraocular pressure is the primary and the only modifiable risk factor of glaucoma.[100] However, the conventional monitoring of intraocular pressure is performed at a doctor's office and is not convenient. Araci's team[100] fabricated an ultra-sensitive microfluidic wearable strain sensor converting small strain changes into a large fluidic volume expansion (Figure 9B). The senor is embedded in silicone contact lenses without using electronic components. They have shown that the detected strain sensitivity can be as low as 0.004%. Similar high sensitivity wearable sensing devices based on microfluidics for monitoring tissue pressures have also been reported by other groups.[53,62]

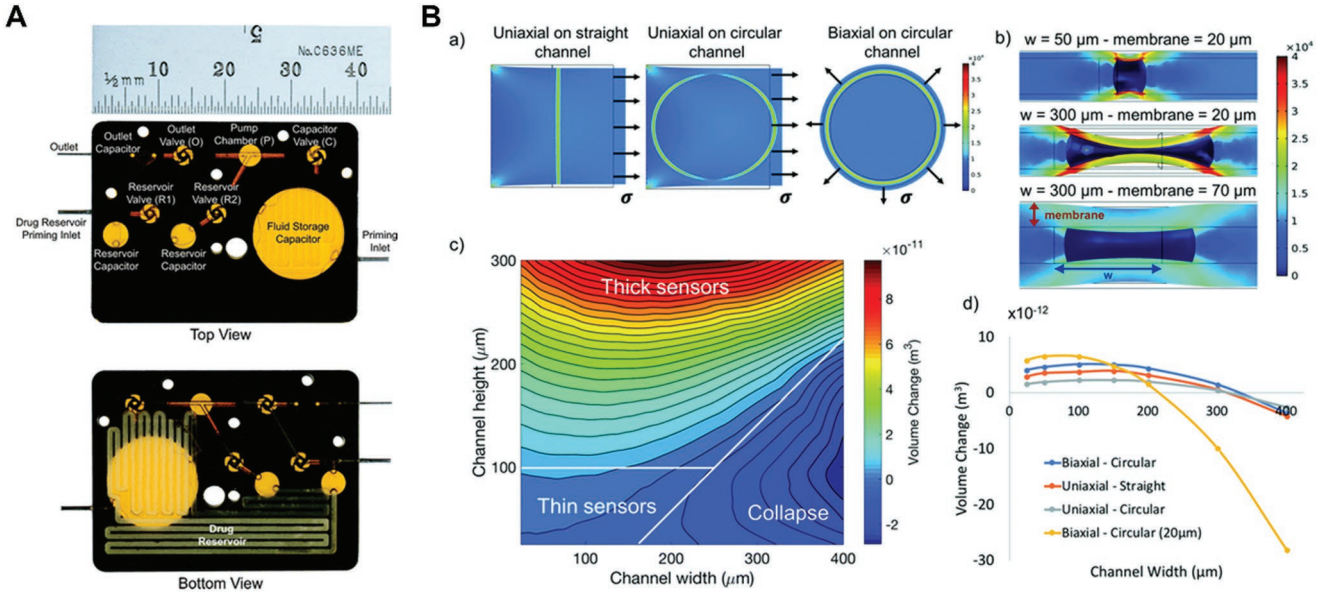

Figure 9. A) Photographs of the microfluidics portion of a micropump for drug storage and delivery. Reproduced with permission.[173] Copyright 2016, The Royal Society of Chemistry. B) Numerical modeling results showing microchannel volume change under strain. Reproduced with permission.[100] Copyright 2018, The Royal Society of Chemistry.

4.2. Exercise/Health Assessment

There has been a large interest in the development of wearable technologies arising from the increasing demands in the areas of fitness and healthcare. Among them, microfluidic-based wearable devices have exhibited great potential applications.

Microfluidics is usually made of polymer materials with superior elasticity, stretchability, and biocompatibility, which keeps them in good conformal contact with human body naturally.[179–181] In addition, the cost of raw materials and fabrication process is low, making it disposable.[120,182] Moreover, microfluidics has strong extensibility and can be integrated with electronics, biosensors, or chemical sensors to achieve functional diversification, especially for human body motion sensing and health monitoring.

For instance, human studies have shown that the secretion of sweat, either its constituents or sweat rate and volume, varies at different regions of body and under different conditions. The sweat rate and volume are higher under vigorous exercise compared with those associated with sedentary activity, and the forearm and lower back tend to yield the highest and lowest sweat level for all conditions.[86] Skin-mounted microfluidic wearable devices for sweat collecting and analysis can help us to quantify such studies or monitoring corresponding physiological signals in real time.[71,86] Moreover, the epidermal microfluidic devices can be waterproofed by sealing with elastomer which can be used in extreme situations, such as running, biking, or swimming (**Figure 10**A).[108]

Biological electricity is also an important indicator for exercise sensing and health assessment. Microfluidic wearable ECG patch[161] can provide real-time heart signal data to help us better adjust the intensity of exercise or warn us when arrhythmia symptom occurs. Similarly, wristband microfluidic pressure/strain sensor can provide real-time pulse information

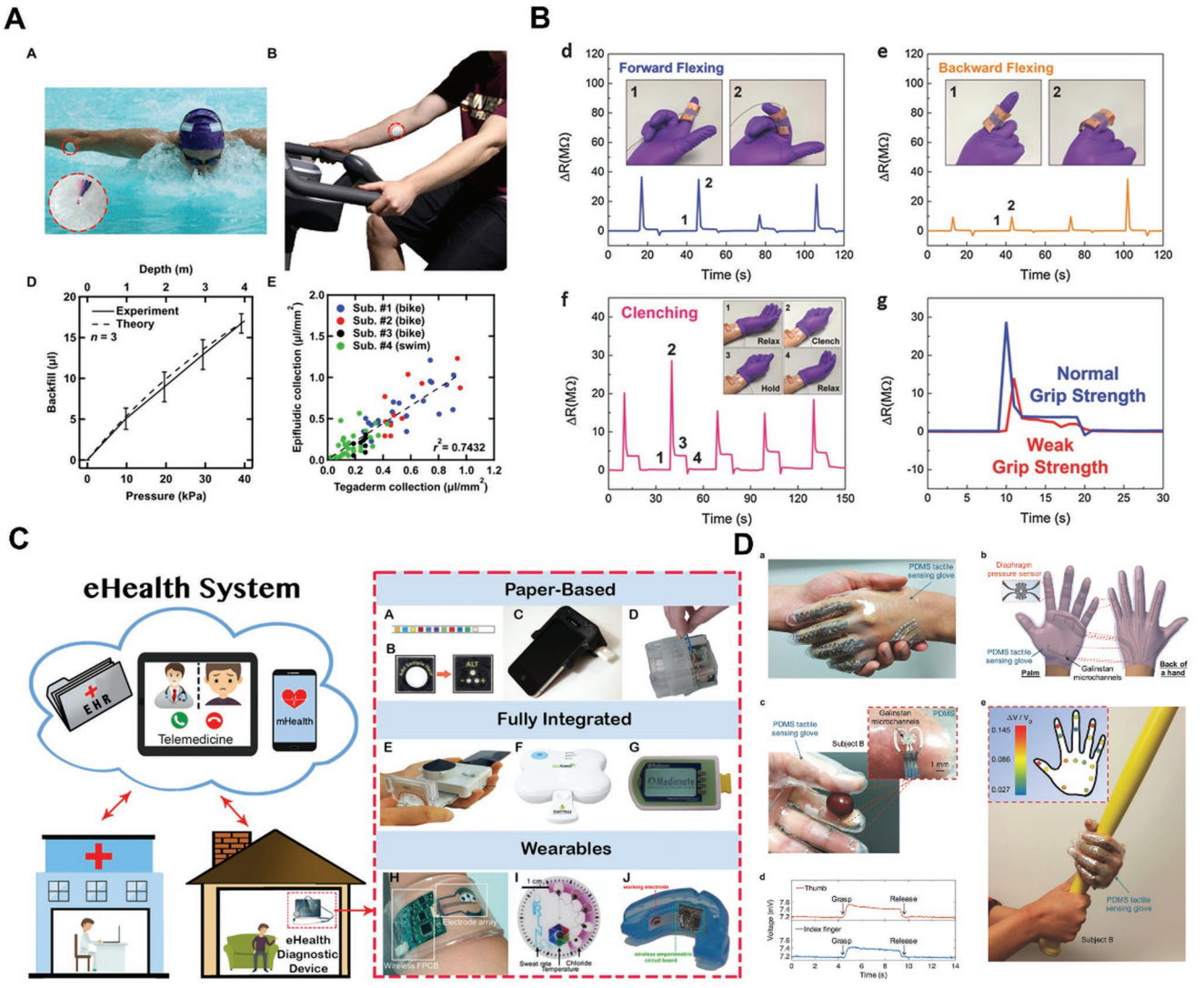

Figure 10. A) Images illustrating the sweat collection from aquatic and dryland athletes. Reproduced with permission.[108] Copyright 2019, AAAS. B) Wearable device for mechanical force sensing and differentiation. Reproduced with permission.[98] Copyright 2016, Wiley-VCH. C) Schematic illustration of the concept of eHealth system. Reproduced with permission.[166] Copyright 2018, American Chemical Society. D) Tactile sensing glove based on microfluidics. Reproduced with permission.[52] Copyright 2017, Wiley-VCH.

during exercise,[52,53,183] and can differentiate movement of fingers (Figure 10B)[98,184] and bending angles of wrist.[99]

In health assessment area, wearable microfluidics can provide early warning or dosing notification of some particular diseases. For example, flow rate[91] or wrist pressure[52] abnormal may be related with hypertension, and intraocular pressure signals[100] may remind glaucoma patient to take medicine.

Microfluidic wearable volatile organic compounds sensor can also be used as safety alerting device to monitor particular gas,[185] and it can notify immediate evacuation once gas concentration reaches its safety limit.

With further integration of wireless communication electronics,[166] the wearable devices based on microscale channels can further turn into eHealth systems for remote monitoring of patients' health (Figure 10C).

4.3. Intelligent Interaction between Human and Devices

With the rapid development of informatization and artificial intelligence, the interaction between human and intelligent devices become more and more significant.[186–188] It requires to translate common human signals, such as voice, gesture, and touch, into electronic signals that a computer can recognize, which is then transmitted to a smart phone or instrumental terminal wirelessly.

Translating gesture language into digital signal has already been realized:[189–191] Lipomi et al.[189] developed a strain sensor comprising a piezoresistive composite of carbon particles embedded in a fluoroelastomer. The sensors, along with digitizers, microcontroller, and a Bluetooth radio were integrated in a glove. This glove is capable of wirelessly translating the American Sign Language alphabet into text displayable on a computer or a smartphone. However, the cost of such a system is close to 100 USD.

Wearable devices based on microfluidics have great potential to achieve similar results at a much cheaper cost. For example, microfluidic tactile diaphragm pressure sensor[52] can convert pressure change into voltage signal (Figure 10D), and it is capable of resolving sub-50 Pa changes in pressure, leading to high sensitivities of a 0.0835 kPa^{-1} change in output voltage. Once such sensors are embedded into a PDMS glove, the tactile information of a human hand when touching or holding objects can be transmitted to intelligent device. Although this approach cannot realize alphabet translating, it has a great potential for further development.

5. Summary and Outlook

In summary, wearable devices integrated with various electronic modules, biological sensors, and chemical sensors for physiological signals monitoring, and clinical diagnosis and therapeutics, have drawn large public attentions. Due to its inherent advantage of microfluidics, such as superior stretchability, elaborate microstructure, high integration of multiple functions, and low cost, it has been widely used in wearable devices.

Well-designed microfluidic devices can realize excellent multiple functions in wearable devices, including sample collecting, handling and storage, sample analysis, signal converting and amplification, mechanic sensing, and power supplying. Moreover, the microfluidic wearable devices with further integration of wireless modules have exhibited potential applications in healthcare monitoring, clinical assessment, and human and intelligent device interaction. However, there are still many challenges that require much endeavor for further development.

One challenge is the multi-parameter and multi-constituent analysis for physiological signal monitoring in a single wearable device. The health status assessment of human body is usually based on multi-parameter analysis. Although present microfluidic wearable sensing systems based on single sampling can realize real-time and precise monitoring for particular biological fluids or electricity, the information provided is not comprehensively enough. Some existing dual sampling wearable system can monitor two biofluids at the same time, but the constituents that can be analyzed are very limited. Dual and even multiple sampling wearable devices for comprehensive parameter analysis of several biofluids is waiting to be invented.

Another challenge is to realize ultrasensitivity and intelligent microfluidic wearable device with its minimal size and low cost. Intelligent products are the future trend of development on body motion monitoring, remote diagnosis and treatment, and human–computer interaction. Currently, there is still a long way to realize such a target, because the sensitivity of most microfluidic devices is not high enough, and the operation of devices normally requires manual intervention.

Despite these challenges, however, the future of microfluidic wearable devices seems promising for realizing next-generation wearable devices with optimized miniaturization, wearability, versatility, and ultrasensitivity. To achieve these goals, a broad cooperation among biologists, physicists, engineers, and clinicians in the microfluidic research will be of vital importance.

Acknowledgements

This work was supported by the National Natural Science Foundation of China grants no. 11604030, no. 11674043, and no. 11974067; by the Fundamental Research Funds for the Central Universities Project no. 2018CDJDWL0011 and no. 2019CDYGYB017; by Hong Kong RGC grants no. GRF 14306518, 14303415, CRF C6004-14G, C1018-17G; and by CUHK Direct Grants 4053313, 4053231, 4053167, and 4053354.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

clinical diagnoses, healthcare, microfluidics, physiological signal monitoring, wearable devices

Received: October 8, 2019
Published online:

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