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Recent advances in noninvasive flexible and wearable wireless biosensors

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ABSTRACT

Flexible and wearable biosensors have great potential to interface with skin and noninvasively extract biofluids for real time and continuous monitoring of physiological status. Soft electronics is the prime factor in these wearables, regardless of sensing mechanism and fabrication technology. Wireless connectivity would be a valuable addition to enhance wearable biosensor's scope for remote and resource limited settings. These skin-adaptable, user-friendly, battery-free (although not all), and noninvasive devices continuously and simultaneously monitor wearer well-being and transfer data wirelessly. Thus, they have a great potential to improve quality of life with timely diagnostics and hence early treatments. However, they remain in the early stages, with relatively conventional sensing modalities, battery requirements, soft electronics fabrication limitations, and practicable size restrictions to retain skin compatibility. We classify wearable biosensors by sensing functionality, such as skin temperature, pH, heart rate, sweat glucose, uric acid, sweat electrolyte, cerebrospinal shunt flow, and toxic chemicals, and discuss challenges and prospects for these biosensors.

1. Introduction

1.1. Autonomous and wearable wireless biosensor necessity

Wearable biosensors based on low modulus flexible substrates provide opportunities for direct attachment to human skin and body movement compliance. The rationale behind conformable biosensors is to enhance noninvasive sample collection reliability (Dang et al., 2018). Noninvasive, quick response, and compact wearable sensors could be utilized in advanced applications, including point-of-care testing and self-health management. Adding wireless power and data transfer capability would greatly enhance wearable sensor scope for remote monitoring and IoT sensing. They can be integrated with wrist bands, headbands, eyeglasses, mouthguards, bandages, smart clothes, wearable gloves, tattoos, stickers, etc. to enable comfortable and continuous monitoring. Wearable wireless biosensors (WWBs) that were convenient to wear and commercially available at affordable cost, providing early diagnostics and subsequent immediate actions for further treatment or lifestyle changes could have enormous impact on human life. Their potential role as therapeutic agents for target sites will be widely investigated in the future.

Health practitioners recommend that diabetes patients monitor blood glucose levels several times a day. However, there are several practical drawbacks to achieve this goal, including inconvenient measurement (invasive, require calibration, and time consuming) and costs associated with blood glucose monitoring (BGM). Furthermore, insulin and essential medicines, e.g. agents that lower blood pressure, have many drawbacks. Eighteen commercially available BGMs devices marketed in USA were recently investigated (Hellmund et al., 2018), selecting trial subjects to cover 90% of commercial systems used by diabetes patients from 2013 to 2015. The triple-blinded survey showed that only 6 (of 18) devices passed all three times and hence were awarded the Seal of Approval (Klonoff et al., 2018).

Several other biosensors and commercial devices monitor bioactivities and dynamic physiological status in addition to BGM. For example, excessive sodium loss in sweat during intense exertion or cystic fibrosis patients, increases illness risks, including hyponatremia. Commercial products to screen cystic fibrosis, e.g. Macroduct and Nanoduct™ neonatal sweat analysis systems by Wescor Nanoduct Laboratory, require collecting a large sweat volume, which is uncomfortable for the user and hinders rapid detection. The bulky and expensive instrumentation is also incompatible with on-body testing, and the sweat samples must be transported after collection, which compromises accuracy.

Deepu et al. (2018) proposed a WWB to measure electrocardiography (ECG) on-chip, and Antolín et al. (2017) proposed one to monitor environmental CO_2. Both devices used conventional brittle printed circuit board (PCB) substrates, which were inconvenient to wear and nonconformable to body parts. Hanitra et al. (2018) proposed analog front-end circuitry to noninvasively detect sweat lactate and

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Li^+. They employed four channel electrochemical detection based on amperometric and potentiometric modalities, and achieved sweat lactate and Li^+ limit of detection LOD = 1.43 and 2.1 mM, respectively. However, although they employed a flexible substrate (Kapton), various hardware components and modules were rigid. Disposable biosensors incorporating flexible substrates and circuitry are greatly demanded to avoid conventional inflexible substrate and circuitry drawbacks and limitations.

Although electrochemical and optical biosensors (fluorometric (Qiu et al., 2017), and colorimetric (Ren et al., 2018b), (Ren et al., 2018a)) have been developed on flexible substrates (Shu et al., 2018), they require labelling steps to amplify the signal (Zeng et al., 2018), and expensive equipment and skilled personnel to fabricate and operate, which are major obstacles for point-of-care (POC) applications (Luo et al., 2019; Yu et al., 2019; Zhao et al., 2017). Yuksekkaya et al. (2015) proposed a highly sensitive, robust, portable, and inexpensive biosensor to diagnose pathogens/cells at POC. Two parallel silver electrode strips on flexible polyester film were integrated with microfluidic channels to detect biomaterials using impedance spectroscopy. However, the proposed biosensor required off-chip sample preparation, including virus capture using antibodies, washing, and virus lysis. This tedious task sequence could be avoided if there were a suitable standalone WWB that could operate autonomously at POC.

Invasive procedures depend upon incisions using a lancet or finger prick to access blood or interstitial fluids, and hence tend to be inconvenient and uncomfortable for patients. In contrast, noninvasive detection employs naturally occurring biofluids already outside the skin barrier, such as sweat, saliva, tears, urine, etc., and hence are generally preferred over invasive detection. Wearable wireless biosensors powered by energy harvesting could be largely independent of external power sources, although some exceptions exist. Resources are rigorously harvested in these WWBs (time, cost, and energy source) compared with inflexible and battery-operated biosensor counterparts. WWBs incorporating all the required features could significantly mitigate the challenges and limitations for conventional biosensors and/or current commercial instruments.

1.2. Flexible materials and manufacturing techniques

To develop a wearable biosensor, Considerable attention must be given to selecting favorable substrates, biocompatibility, functional/active material, and lowest cost manufacturing technique(s). Stretchability has been an important focus for skin compatible electronics. Intrinsically stretchable materials (elastomers, polymer composites, and elastomer composites with metallic fillers) provide mechanical robustness, high device density, and scalability. The core concept is to introduce strain dissipation mechanisms into the material design. Self-healing electronic materials have been a strong secondary focus, with dynamic intermolecular interactions providing the most efficient self-healing capabilities for polymeric electronic materials (Wang et al., 2018). For example, polyimide, polyethylene terephthalate (PET), Polyethylene naphthalate, polyurethane, and poly (styrene-block-(ethylene-*co*-butylene)-block-styrene) have been used to realize wearable biosensors. Parylene (thin film polymer) is another commonly used biocompatible coating material; and silicone (Polydimethylsiloxane (PDMS), and Ecoflex), paper, silk, and textile have been popular substrate choices previously. Ecoflex Young's modulus closely matches human skin, providing a suitable and widely used option (Heikenfeld et al., 2018). PDMS and Ecoflex have remarkable elongation limits (420% and 900%, respectively; An et al., 2017). The most commonly used active materials include carbon nanotubes, graphene, silver nanoparticles, and PEDOT (Liu et al., 2018). Chen et al. (2017) proposed a stretchable antenna for wearable devices by screen printing an Ag-PDMS composite to provide soft RF transmission line and antenna. This provided efficient structure at low cost, and achieved 1000 S/cm conductivity for the stretchable conductor.

Wearable biosensors are commonly fabricated using pattern transfer techniques, such as lithography; and screen, inkjet, and 3D printing, which can realize fine resolution patterns on elastomeric substrates. Composite characteristics strongly depend on doping concentration and distribution state. For example, carbon black-silicone composite provides high electrical resistance for low carbon black concentrations (0.08–0.09 wt%), which decreases when concentration exceeds 0.14 wt % (Liu et al., 2018).

Materials used to develop flexible sensing systems exhibit more durability compared with inflexible systems that rely on rigidity and brittleness. The former also achieve better performance in terms of sensitivity, reduced power consumption, and dynamicity compared with rigid substrates, and have relatively low cost which is highly advantageous for large scale production (Nag and Mukhopadhyay, 2017).

Thus, key considerations for wearable biosensor design can be summarized as follows.

1. Low modulus flexible substrates provide excellent options to realize stretchable and bendable sensors.
2. Substrate thickness is crucial and application dependent. For example, ECG, respiration rate, and limb movement sensors demand ultrathin substrates due requiring response sensitivity and smooth placement against skin during movement.

Nanoparticles have been used to develop stretchable electrodes on flexible substrates due to providing superior aspect ratios, surface to volume ratios, and flexibility/bendability. Different nanoparticles and nanocomposites (nanowire, nanoribbon, nanotube, etc.) offer different surface area, thermal, mechanical, and electrical properties. Selected nanoparticles are generally functionalized to enhance their mechanical properties, influencing stabilization and oxidation steps. Gold nanoparticles are the most commonly employed functionalization, commonly employed for gene detection and bioimaging (Nag and Mukhopadhyay, 2017).

1.3. Adding wireless power and data transfer

Gigahertz to terahertz electromagnetic waves can pass through cell membranes with little or no loss (Salim et al., 2018), subsequently interacting with cytoplasm to provide distinct dielectric behaviors for healthy and malignant cells. For example, Porter et al. (2016) proposed a wearable microwave biosensor to detect breast cancer. The proposed biosensor comprised a flexible substrate (50 μm Kapton polyimide) with 16-element 20×20 mm antennas asymmetrically embedded in clothing (bra) to provide the wearable interface. However, the embedded antennas were delicate and required a switching matrix to connect each pair individually to sensing array ports with a vector network analyzer for measurement, which was somewhat time consuming. The sensing array overall form factor was also incompatible with contemporary wearable biosensors.

Soft electronics alone are insufficient to develop wearable skin compatible biosensors. For example, commercially available pacemakers have 5–15 year battery lifetime, with periodic surgery required to replace discharged batteries (Jaemin Kim et al., 2017a,b). Self-contained power is essential for implantable and WWBs.

Near field communication (NFC) is contactless short-range communication that enables smartphones and related chipsets to exchange information in the unlicensed RF industrial scientific medical (ISM) band at 13.56 MHz. The NFC working principle incorporates electromagnetic induction between loop/coil antennas to simultaneously transfer power and data. This removes, or at least reduces, battery requirements, enabling further miniaturization (Jaemin Kim et al., 2017a,b). Bluetooth, custom designed NFC tag readers, and radio frequency identification (RFID) are common short range communication protocols. Although NFC enabled devices must be within the appropriate range, e.g. a few meters for Bluetooth, one advantage is that they

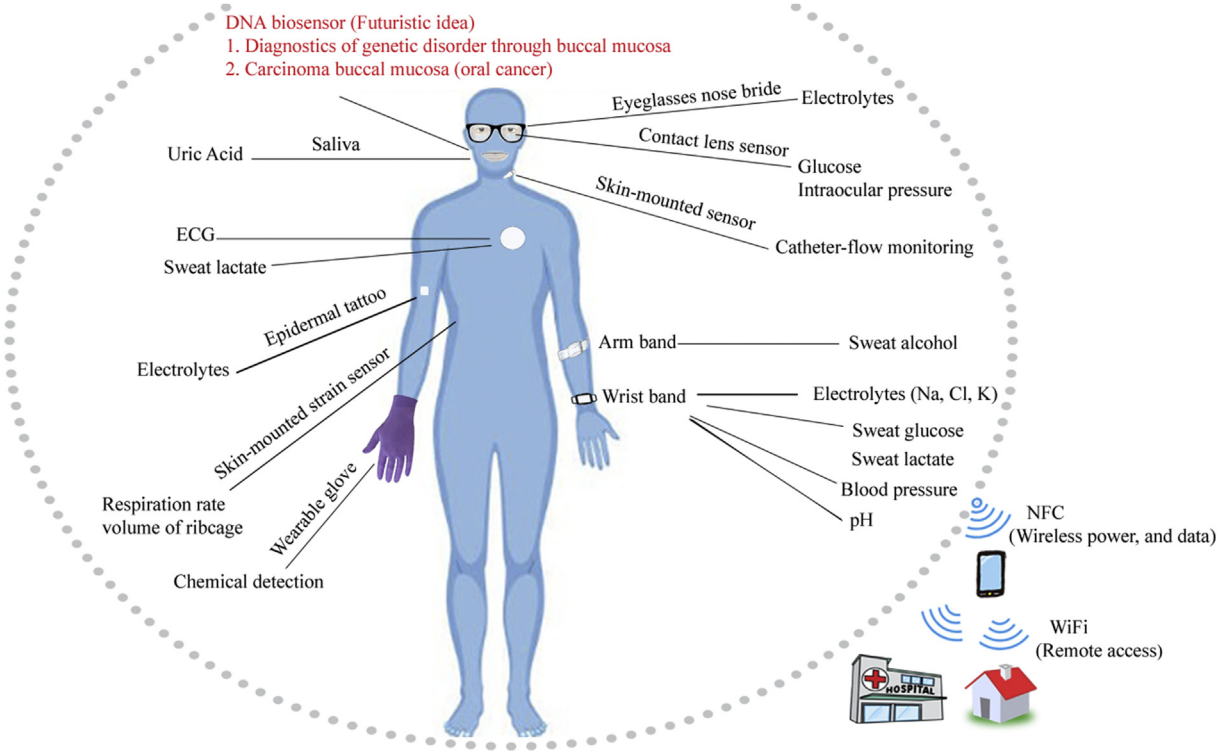

Fig. 1. Noninvasive flexible wearable wireless biosensors: autonomous, user-friendly, skin-compatible, and noninvasive health monitoring devices. The suggested DNA biosensor is a future concept, not yet implemented, all others are currently available.

do not require specific receiver designs, with a range of receivers being suitable. Consequently, NFC has been employed for various WWBs to transfer sensed data wirelessly without requiring line-of-sight (LOS). Wireless charging systems can significantly extend battery lifetime, enabling longer timescale bioactivity monitoring (Ha et al., 2018). Fig. 1 summarizes current noninvasive flexible and WWBs.

2. Flexible and wearable wireless biosensor classification

Health practitioners commonly use pH to monitor acid/base imbalance. Human metabolic processes regulate O_2 and glucose into blood and H^+ and CO_2 out of blood to maintain pH, and variation can cause or indicate various physiological disorders, including sepsis, heart attack, kidney failure, congestive heart failure, or uncontrolled diabetes. Anomalous sweat electrolyte concentration has been correlated with several diseases, e.g. glucose, lactate, urea, Ca^{+2}, K^+; and pyruvate can be used to diagnose/monitor diabetes, liver disease, renal dysfunction, hypocalcemia, ocular disease, and hypochloremia (Dang et al., 2018).

Various wearable biosensors have been proposed to determine metabolic parameters, including electrolytes, glucose, pH, and lactic acid; vital signs, including breathing and heart rate, blood pressure, wrist pulse, ECG, and skin temperature; and body motions, including hand and finger movements, facial expressions, vocal cord, etc. There is an increasing trend to develop simultaneous multivariate sensing platforms on a single chip.

2.1. Multivariate sensing through sweat

2.1.1. Glucose, lactate, Na+, K+, and skin temperature

Gao et al. (2016) proposed a fully integrated sensor array (FISA) to simultaneously detect glucose, lactate, Na+, K+, and skin temperature, as shown in Fig. 2(a)–(d). The proposed wearable sensing array was mechanically flexible due to the polyethylene terephthalate (PET) substrate. Amperometric glucose and lactate sensors employ glucose and lactate oxidase, respectively, which were immobilized within a polysaccharide chitosan film. An Ag/AgCl electrode was utilized as the shared reference and counter electrode for both sensors. Reduction potential was reduced to 0 V using Prussian blue dye to activate the sensors without requiring external power. Current signals corresponding to metabolite concentration differences between electrodes were autonomously generated, and Na+ and K+ levels were measured using an ion selective electrode, coupled with a polyvinyl butyral (PVB) coated reference electrode. The ion selective electrode was used to quantify ion selective activity in the potentiometric biosensor. Target ions interact with the corresponding ionophores in an ion–exchange membrane, causing measurable voltage changes. A resistance based temperature sensor was developed using Cr/Au metal microwires with parylene insulating layer between the metal lines, skin, and sweat to ensure reliable readings, and a transceiver to transfer data wirelessly to mobile handsets using Bluetooth.

Measured glucose and lactate sensitivities were 2.35 nA μM^{-1} and 220 nA mM^{-1}, respectively, and the proposed sensor exhibited consistent repeatability over four weeks. Bending tests indicated minimal changes in FISA response, and site-specific (wrist and forehead) metabolite and electrolyte level variations were monitored and analyzed.

2.1.2. Glucose, lactate, sweat rate/loss, chloride, and pH

Various real-time body-worn sensors for sweat analysis have been developed based on electrochemical, amperometric, and potentiometric techniques, including intricate circuitry for signal generation and data transmission (Bluetooth), and rechargeable batteries for power. However, the modules are difficult to miniaturize, which dictates the overall form factor, resulting in incompatible size and weight for skin attachment (Bandodkar et al., 2019). Wearable sweat sensors based on electrochemical detection require non-ideal form factors, and colorimetric based sweat sensing is prone to semi-quantitative operation and measurable biomarker limitations. Although potentiometric sensors embody wireless, and battery-free electronics, their sensing capability is limited to electrolyte levels and hence cannot detect other physiologically relevant species, such as metabolites, drugs, and proteins.

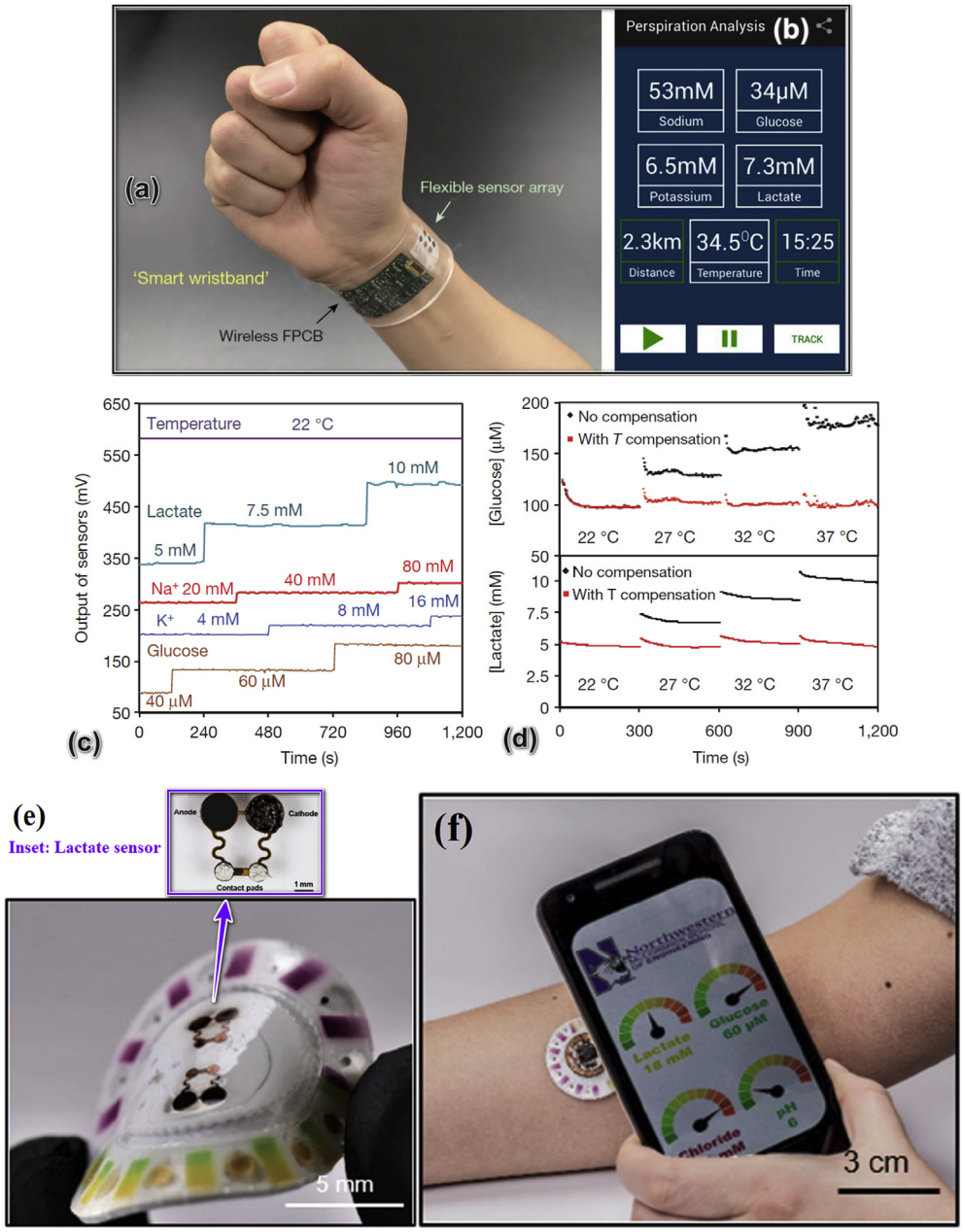

Fig. 2. (a) Example wearable flexible integrated sensor array (FISA), (b) real-time data for sweat analyte levels and skin temperature during exercise; (c) FISA selectivity with respect to analyte concentration, (d) glucose and lactate measurement stability and accuracy with respect to temperature variation; (e) battery-free hybrid microfluidic/electronic patch with embedded sensors (inset: lactate sensor); (f) mobile phone interfaced with hybrid patch to collect and display wireless data.

Bandodkar et al. (2019) proposed a hybrid sensing system comprising chronometric microfluidics incorporated with colorimetric assays. The sensor was thin, with a skin-compatible form factor, and achieved real-time noninvasive sensing for glucose, lactate, and chloride concentrations simultaneously with sweat rate/loss, and pH (see Fig. 2(e)–(f)). The electrochemical sensing mode was inspired by biofuel cell function, eliminating the need for a potentiostat and allowing simple circuitry, in contrast to current amperometric sensors. Consequently, miniaturized and low-cost NFC modules can be employed for sensing and data transfer purposes. Figure S1 shows further sensor construction details.

2.1.3. Lactate and potassium

Sempionatto et al. (2017) proposed a wearable multi-analyte glass (MAG) chemical sensing platform to monitor sweat lactate and potassium using potentiometric and amperometric sensors simultaneously and noninvasively, integrated into eyeglass nose bridges. Each sensor was connected to a PCB on each side of the MAG frame inner arms. Each PCB collected data individually and simultaneously from the corresponding sensors and wirelessly transmitted them to a laptop via Bluetooth. The replaceable sensor stickers could monitor a wide variety of electrolytes. Lactate biosensor screen printed electrodes were realized on a flexible PET sheet as follows.

- Ag/AgCl ink was used to fabricate the reference electrode, and the current collector to measure response;
- Prussian blue/graphite ink was used to fabricate the working and counter electrodes.

Potassium sensors were screen printed on a flexible PET sheet:

- The g/AgCl ink was used fabricate reference electrode and current

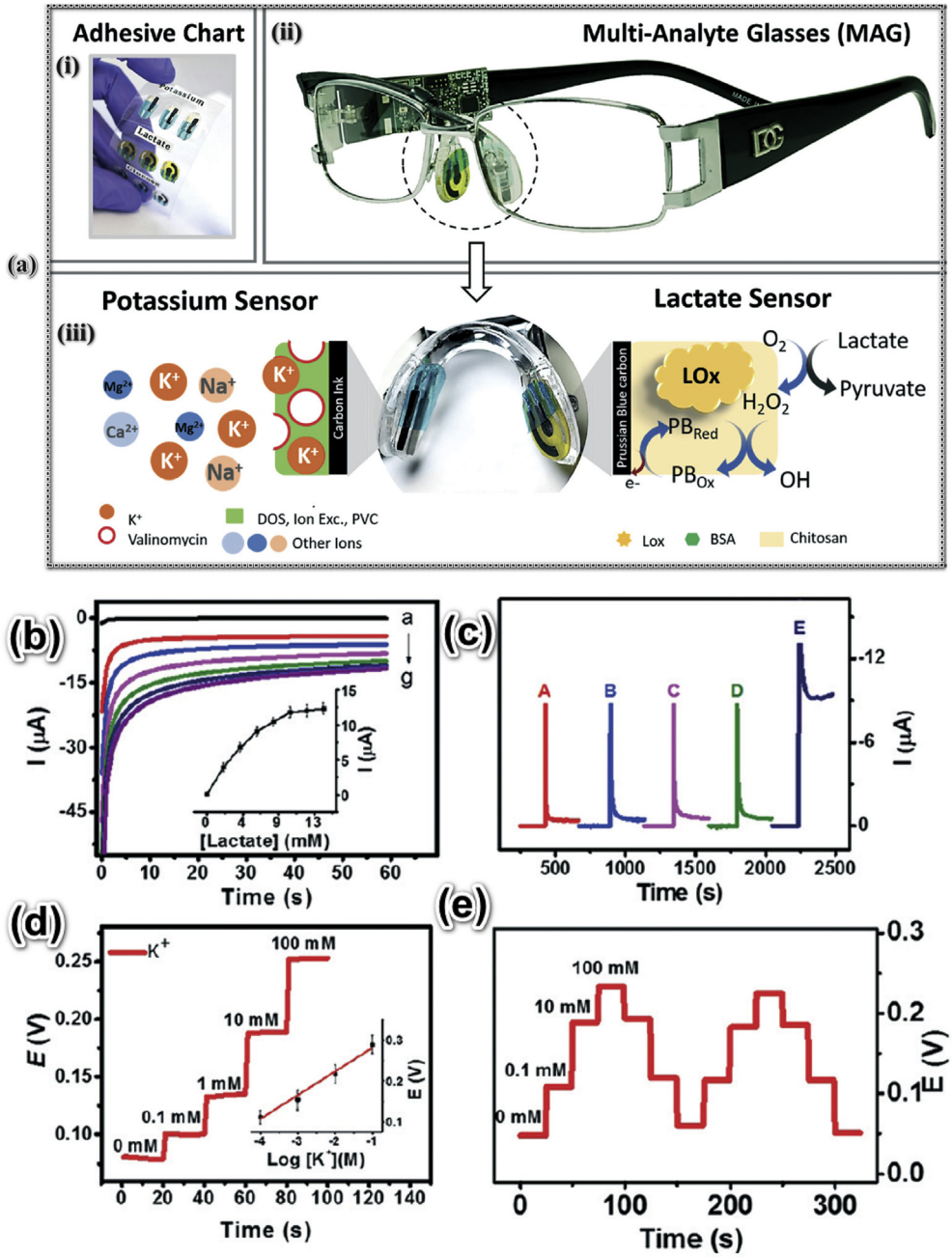

Fig. 3. (a) Multi-analyte glasses: (i) screen printed sensors as interchangeable stickers, (ii) MAG integrated with wireless PCBs along the arms, (iii) nose pad electrochemical potassium (left) and lactate (right) sensors with corresponding recognition and transduction events; (b) chronoamperometric response for 0, 2, 4, 6, 8, 10, 12, and 14 mM lactate with the corresponding calibration (standard deviation = 3); (c) selectivity to (A) 84 μM creatinine, (B) 10 μM ascorbic acid, (C) 0.17 mM glucose, (D) 59 μM uric acid, and (E) 4 mM lactate; (d) potassium sensor KCl response with corresponding calibration profile; (e) potentiometric sensor hysteresis for various potassium concentrations.

collector;
- conductive carbon was used to fabricate the working electrode.

Electrode modification in the lactate and potassium sensors was achieved using.

- Lox, BSA, Chitosan, and
- Valinomycin, DOS, Ion. Exc., PVC.

PCBs on each frame arm controlled sensor operation and transmitted data wirelessly to the host device. The proposed sensing platform offered fast response, selectivity, reproducibility, and wide dynamic range, as shown in Fig. 3(a)–(e).

2.1.4. Lactate and electrocardiogram

Imani et al. (2016) proposed a hybrid wearable chemical-physiological patch to simultaneously measure sweat lactate and ECG with a single platform. The hybrid patch was screen printed on a 50 μm flexible polyester film to realize a conformable sensor which could be attached to human skin without discomfort. Bipolar ECG electrodes require 1–6 cm minimum separation to attain high quality signal, hence they employed a printed hydrophobic layer (using Ecoflex) to separate the three amperometric and corresponding Ag/AgCl electrocardiogram electrodes, maximizing biosensor stability in the presence of excess perspiration. Two sensors and additional circuitry to facilitate wireless telemetry (Bluetooth) were integrated on a PCB, realizing a wearable wireless potentiostat, as shown in Fig. 4(a) and (b). The proposed biosensor reacted with lactate to catalyze lactate oxidation, generating pyruvate and H_2O_2. Since Prussian blue ink is selective towards H_2O_2, they printed the working electrodes with it and used Ag/AgCl ink to print the reference electrode. The hybrid patch was tested on the chest region (V1–V6 lead placement), since it was a convenient site to monitor ECG and sweat rate during physical excursion.

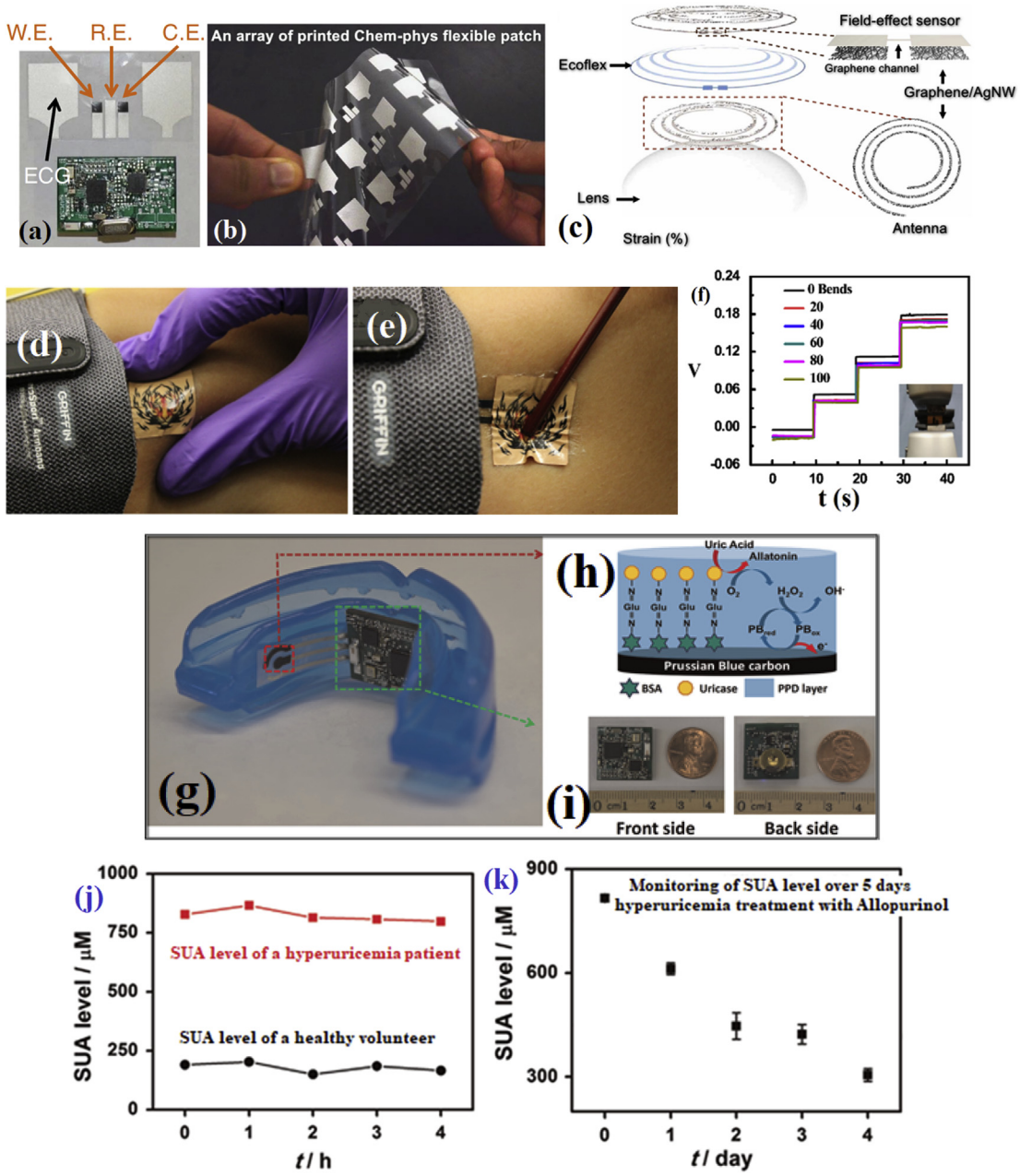

Fig. 4. (a) Wearable chemical-physiological hybrid biosensor with wireless electronics and (b) corresponding screen printed array; (c) Wearable soft contact lens sensor, integrating glucose and intraocular pressure sensor; (d) transferable tattoo sensor for sodium detection subjected to pinching and (e) poking after attaching to the skin, with (f) subsequent repeatability and stability; (g) mouthguard biosensor integrated with wireless amperometric circuit board; (h) chemical modification of Prussian blue carbon working electrode (WE): uricase enzyme immobilized by crosslinking with bovine serum albumin and glutaraldehyde; (i) wireless amperometric circuit board; Salivary uric acid (UA) level monitoring over (j) 5 h, and (k) 5 days showing the effect of hyperuricemia treatment with Allopurinol®. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2.2. Multivariate sensing through tears

2.2.1. Glucose level within tears and intraocular pressure

Tears are a complex extracellular fluid containing proteins/peptides, lipids, electrolytes and metabolites from lacrimal glands, ocular surface epithelial cells, goblet cells, Meibiomian glands, and blood (Bandodkar and Wang, 2014). Therefore, they offer a good alternative fluid source for noninvasive monitoring. However, conventional in-vitro tear analysis poses several challenges, including evaporation of collected tears (commonly 5–10 μl) during transport to laboratories, potentially compromising analysis accuracy; and extreme care and sophisticated techniques are required during sample collection due to the delicate nature of the human eye.

Kim et al. (2017)a,b proposed a transparent and stretchable sensor on a wearable soft contact lens to simultaneous and independently monitor glucose level within tears, and intraocular pressure through the device's resistance and capacitance, as shown in Fig. 4(c). The sensing device was realized using an array of 9 field-effect transistors (FETs) comprising a graphene channel and hybrid source-drain (S/D) electrode. Glucose oxidase (GOD, β-D-glucose) was immobilized on the graphene channel using a pyrene linker via p–p stacking to provide selective and sensitive glucose detection. Atomic force microscopy confirmed selective binding of GOD to the graphene channel surface. The detection mechanism for glucose was catalytic oxidation of glucose to gluconic acid and reduction of H_2O to H_2O_2. Charge carrier concentration in the channel, and thus the drain current, increases for

increasing glucose concentration. Hybrid graphene-Ag nanowires were utilized due to their high transparency (> 91 %) and stretchability (~25%), providing reliability, comfort, and unobstructed vision when the proposed contact lens was placed on the eye. Connecting the wires was impractical to power the device and acquire sensor responses, hence wireless technology was adopted for power transfer and data transmission. Hybrid material electrodes and the graphene channel were lithographically patterned on ultrathin parylene (~500 nm). Parylene was preferred over other plastic materials due to its intraocular biocompatibility and mechanical superiority. All device components were transparent, with slightly visible spiral antenna, and conformably conformed to the curved contact lens. In-vivo and in-vitro tests were conducted using live rabbit and bovine eyeballs, confirming the hybrid FET structure feasibility on PET and PDMS substrates, stretching up to 25% uniaxial tensile strain. The very slight resistance variation ($\Delta R < 6\%$) even after 5000 stretching cycles (25% tensile strain) confirmed the graphene-AgNW hybrid as a promising option for wearable electronics on soft contact lenses. Minimum detectable glucose concentration from the proposed device (1 mM) was 10 fold improvement over previously reported contact lens sensors fabricated from metal evaporated electrodes.

2.3. Single analyte wearable wireless biosensors for detection of metabolic parameters

2.3.1. pH detection

Dang et al. (2018) proposed a stretchable wearable pH sensing system comprising a pH sensor and RFID antenna. The stretchable RFID antenna included 4 turns of square coils on flexible polyimide film, achieving frequency tuning to 13.56 MHz using coil inductance and tuning capacitors. The pH sensing electrode (SE) material was a graphite-polyurethane composite, providing superior flexibility and response time compared with metal oxide electrodes. These composite materials exhibited outstanding performance for biosensing applications, and could be operated and fabricated at low temperatures (80 °C) consistent with the stretchable substrate. Battery-free operation was achieved using energy harvested from electromagnetic waves emitted from the RFID reader.

The reference electrode (RE) and substrate were realized using Ag/AgCl and PDMS, respectively, with optimum 1:1 ratio graphite:polyurethane to balance between printability and conductivity. Serpentine shaped stretchable COMSOL interconnects were selected considering the maximum stretch exhibited by the pH sensor. SE and RE were deposited on the interconnect contact pad, and the sensor assembly was subsequently enclosed in PDMS. Solutions of pH buffer, Dulbecco's modified Eagle medium, and human sweat equivalent (NaCl, KCl, and lactic acid in deionized water) were prepared to evaluate pH sensor performance. The solution's provided pH range 5–9, and sensor response between the two electrodes was 80–160 mV, with 8 s response time. SE and RE were connected through stretchable interconnects capable of withstanding up to 53% strain, whereas human skin has average maximum strain ≈ 30%. Therefore, the proposed stretchable pH sensing system could be conformably attached to the skin without compromising electrical performance.

2.3.2. Electrolyte detection

Bandodkar et al. (2014) proposed an epidermal tattoo based potentiometric sensor to noninvasively monitor sodium concentration in perspiration, as shown in Fig. 4(d)–(f). Real-time sweat sodium profile was wirelessly transmitted from a body worn transceiver to an internet connected device (notebook, smartphone). An insulating coating with a tiger face tattoo was realized using screen and laser printing techniques, respectively, and the sensor was calibrated with NaCl solutions. Ten healthy subjects were then asked to cycle for 30 min to validate the tattoo performance. Selectivity for sodium in the presence of other electrolytes, 100 bending cycles, stretch (26 %), and number of pokes were assessed using standard NaCl solution (0.1–100 mM).

2.3.3. Sweat alcohol detection

Transdermal alcohol concentration (TAC) could be an alternative approach to estimate blood alcohol concentration (BAC) because human perspiration can contain trace amounts of alcohol after alcohol consumption (Swift, 2000). (Leffingwell et al., 2013) proposed a wearable transdermal alcohol sensor, but detection was time consuming (0.5–2 h) compared with BAC estimation using breath analyzers. Transdermal approaches to monitor physiological parameters have been categorized as partially invasive (Heikenfeld et al., 2018), since they require a non-natural opening through the skin.

Kim et al. (2016) proposed a wearable tattoo based iontophoretic flexible biosensor for noninvasive alcohol monitoring. The transdermal patch delivered pilocarpine to induce sweat and employed iontophoresis and amperometric detection of ethanol in the generated sweat using alcohol oxidase enzyme and Prussian Blue electrode transducer. Sensed data was wirelessly transmitted via Bluetooth. This skin-worn low-cost sensor integrated sweat inducing iontophoresis and amperometric enzymatic biosensing domains in a single platform with flexible electronic circuitry. Integration was achieved by adding a pair of conductive Ag/AgCl iontophoretic electrodes to the three-electrode amperometric system. All electrodes were screen printed on tattoo paper, providing easy skin attachment and removal and low sensor cost. Both the sensor and printed electronic circuit (for wireless transmission) were flexible and consistent with epidermis characteristics (non-planar, and subject to deformations).

2.3.4. Lactate detection

Currano et al. (2018) proposed an organic electrochemical transistor on flexible Kapton film as a WWB to detect sweat lactate. PEDOT:PSS based S/D and gold gate electrodes were connected through the electrolyte solution. The lactate/lactate oxidase redox reaction occurred at gate electrode after modification and immobilization, reducing its potential, which could be sensed as S/D current change. A thin film lithium ion battery was attached to the Kapton film, but it had limited lifetime (~40 min) due to remaining active during sleep mode. The proposed sensor achieved lactate LOD = 1 mM.

Abrar et al. (2016) proposed a flexible lactate sensor with a cross-serpentine shaped conductive electrode fabricated from Ag nanoparticles modified with Bovine serum albumin and glutaraldehyde crosslinking agent. Nafion membrane was incorporated onto the working electrode to study interference by introducing ascorbate. The sensor was fabricated using direct stamping and spray coating, due to its superior performance over inkjet printing in terms of flexibility and increased density. The NFC equipped sensor sensitivity = 262 $nA\,mM^{-1}.cm^{-2}$, and the electrodes showed insignificant wear effects after repeatedly bent with 8 mm bending radius for 10000 cycles.

2.3.5. Uric acid detection through saliva

Uric acid (UA) is the final oxidation product from purine metabolism in the human body. Impaired renal excretion accumulates high UA levels within the body, leading to Hyperuricemia. Irregular UA levels is a biomarker for various diseases, including hyperuricemia, gout, Lesch-Nyhan syndrome, and renal syndrome. Higher UA levels also imply higher type 2 diabetes risk. Kim et al. (2015) proposed a wearable mouthguard wireless biosensor screen printed on a flexible PET substrate for noninvasive salivary UA monitoring, as shown in Fig. 4(g)–(k). Saliva is a complex matrix with high viscosity, high protein concentration, and electroactive species. Therefore, electrode modification is highly desirable to monitor continuous and direct electrochemical measurements. O-phenylenediamine membrane and Prussian blue materials were utilized to provide high selectivity. High correlation between blood and salivary UA has been previously established (Soukup et al., 2012), hence salivary UA level indicates blood UA

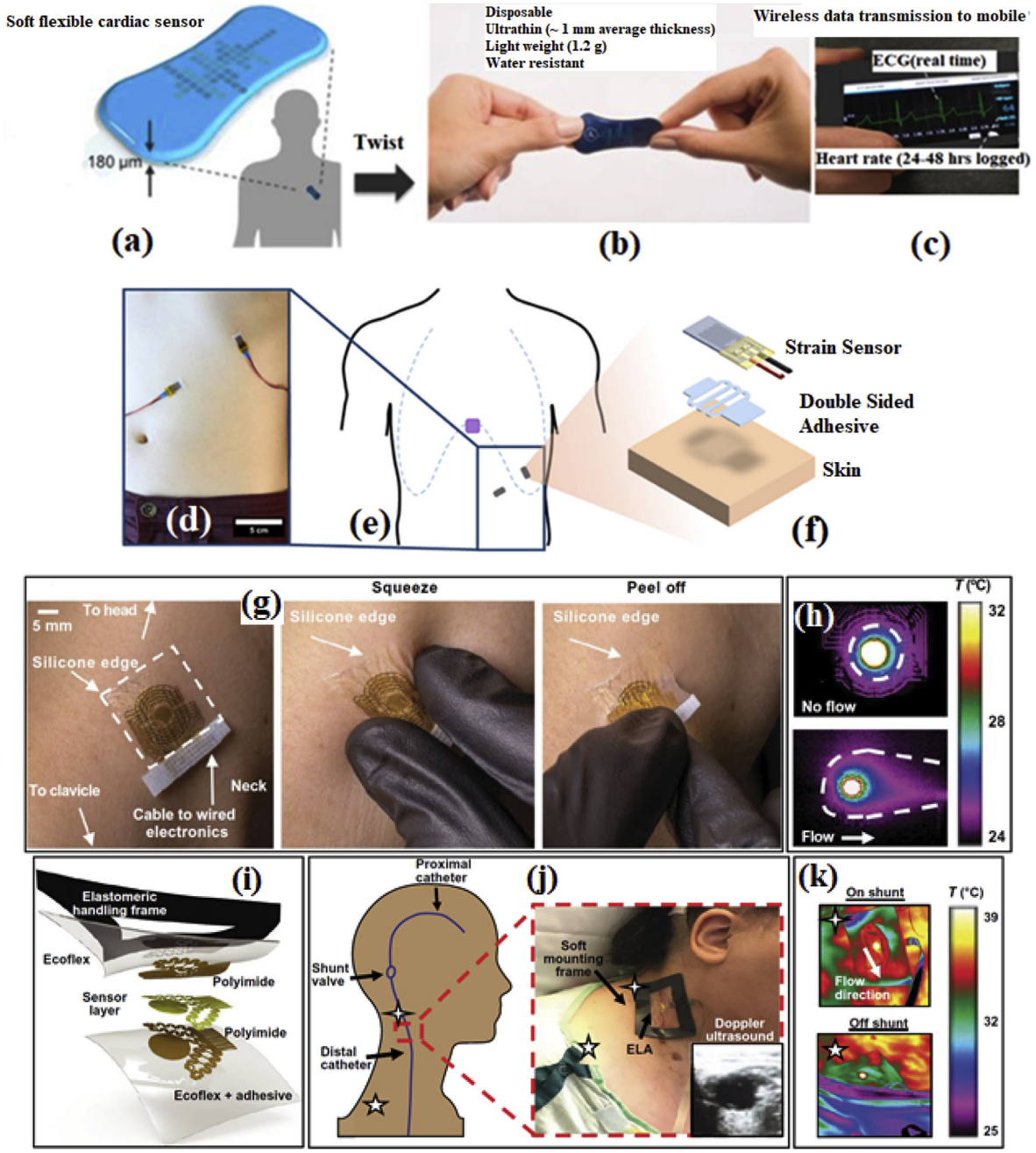

Fig. 5. Soft flexible cardiac sensor: (a) attached to the human chest, (b) mechanical twist, and (c) wireless data transmission to smartphone (via NFC) to visualize logged heart rate data and real-time ECG waveforms; (d) strain sensors on ribcage and abdomen; (e) typical accelerometer (purple square) and strain sensor (gray rectangles) placement; (f) strain sensor and double-sided tape exploded view for skin attachment. Epidermal linear array (ELA) to measure quantitative flow through cerebrospinal shunt: (g) ELA over a shunt during deformation to illustrate robustness of the soft adhesion, device adhered to the skin on a seated subject 2 cm above the clavicle, showing the edge of the silicone substrate (arrows); (h) thermal actuator (purple dashed line), with enlarged images showing stretchable, serpentine interconnects (bottom left, blue dashed line) and individual resistive temperature sensors (bottom right, red dashed line); (i) ELA exploded view; (j) Patient trial: illustration (left) and image (right) for on and off-shunt ELA positioning (inset: Doppler ultrasound image of catheter under the skin at on-shunt location); (k) IR images at on and off-shunt locations indicating locally increased temperature induced by the actuator, and characteristic teardrop shaped heat distribution caused by flow. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

level, providing a noninvasive alternative.

2.4. Single analyte wearable wireless biosensors for detection of vital signs

2.4.1. Electrocardiogram (ECG) and heart rate monitoring

Heart rate (HR) is commonly monitored to assess patient mental and physical state and/or corroborate serious illness, with ECG being the most common technique to detect depolarization signals from the heart muscle, using a sensor comprising two wearable electrodes placed on the sternum. However, signal intensity significantly decreases as the electrodes approach each other (Khan et al., 2016).

Lee et al. (2018) proposed an ultrathin (~1 mm), highly flexible wearable wireless cardiac sensor to monitor real-time ECG waveforms and HR, as shown in Fig. 5(a)–(c). Flexible electronics and battery were placed on a flexible polyimide substrate with foam spacer layers on each side. Two adhesive selectively coated conductive hydrogels were

employed to contact the skin with sufficiently separated electrodes to capture standard PQRST waveforms. The final sensor was disposable, light weight (1.2 g), and comparable size to standard adhesive bandages (58 × 25 × 1 mm), providing an attractive option for ambulatory care. They evaluated patients with atrial fibrillation, and showed that the proposed sensor physical attributes and performance were comparable or superior to commercial Holter monitor results.

Sekine et al. (2018) proposed a flexible pressure sensor to monitor pulse rate from the wrist and neck. The fully printed, compact (~4 mm^2) and thin (~3 μm) sensor was fabricated using Ferroelectric polymer P(VDF-TrFE) as a pressure detecting layer. P(VDF-TrFE) was selected due to it being soluble in polar solvents and suitable for printing. PEDOT:PSS was screen printed to realize top and bottom electrodes across the P(VDF-TrFE) layer, and the whole assembly was rendered on a 50 μm thick polyethylene naphthalate (PEN) substrate. A Bluetooth low energy module with operational amplifier, chip capacitor, and chip resistor were mounted on the polyimide substrate to wirelessly transmit the sensed data.

2.4.2. Respiration rate and volume monitoring

Chu et al. (2019) proposed a disposable wearable wireless strain sensor with smaller footprint than a bandage to detect respiration rate and volume when placed on the abdomen and ribcage, as shown in Fig. 5(d)–(f). The proposed sensor comprised a piezo-resistive metal thin film in a silicone elastomer layer. The working principle was that the strain change caused proportional resistance change in the metal thin film. The thin film itself contained integrated wrinkles to not only relieve strain (156–226%) but also to help control crack propagation.

2.5. Single analyte wearable wireless biosensors for body motion detection

2.5.1. Wrist flexion, vocal cord, finger, and facial muscle movements

Several smart gadgets have been developed as fitness or activity trackers. These wrist/head-band devices utilize SIM cards to access the internet and can be synchronized with smartphones using Bluetooth. However, their capabilities are limited to pedometer, and/or fitness tracking (blood pressure, and heart rate etc.).

Jeong et al. (2017) proposed a skin-attachable sensor using liquid GaInSn for wireless human motion monitoring, such as vocal cord movements during swallowing and speaking. Strain sensors, antenna, and interconnections in the sensing platform used liquid metal, providing stretchable gel-like characteristics. A battery-free device with diameter < 2 cm was realized using selective wetting properties of reduced GaInSn. The tuning capacitor, resistor, and NFC chip resided in a three layer structure incorporating liquid metal patterns between two PDMS layers. Uniaxial tensile and compressive strain measurement, and some other complex deformation modes, were achieved, including wrist flexion, and vocal cord and finger motions. A commercial NFC reader was used for data capture at 5 mm distance to demonstrate device measurement. Stable performance was achieved over 10000 stretching cycles under 30% strain, confirming excellent sensor durability.

Kou et al. (2019) proposed a wireless pressure sensor using graphene-PDMS sponge as the dielectric layer. The fabricated sensor satisfied mechanical stability, flexibility, and sensing performance for finger bending and facial muscle movements, with possible further applications including bionic-electronic skin and wearable electronic devices.

2.6. Cerebrospinal shunt flow monitoring

Ventricular shunts are a standard method for hydrocephalus diagnostics and treatment, a common and costly neurological illness. Current diagnostic tools to monitor shunt failure have significant disadvantages, including high cost, poor accuracy, inconvenience, and safety concerns. For example, magnetic resonance imaging typically costs $3000 per case, can interfere with magnetic shunt valves, and has limited availability hence typically requiring long wait times.

Krishnan et al. (2018) proposed a noninvasive, skin-mounted, wearable sensing platform to address these problems when assessing cerebrospinal shunt flow utilizing arrays of thermal sensors and actuators for precise, continuous, or intermittent measurement. The proposed sensor was physically robust and easy to use, as shown in Fig. 5(g)–(k), with fabrication exploiting cutting edge technology and materials to realize an ultrathin, soft, lightweight, and skin-like sensor. The sensing platform comprised a central thermal actuator surrounded by 100 precision temperature sensors, placed over the skin with an intermediate polyimide film. Five adult shunt recipients with diverse etiologies were tested and compared with current technologies to develop the proposed system. The final device was validated in vivo with quantitative flow rate determination.

2.7. Chronic wound monitoring

Farooqui and Shamim (2016) proposed low cost wireless monitoring for chronic wounds using a standard bandage form factor. The disposable bandage contained inkjet printed sensors to monitor irregular bleeding using a capacitive sensor, pH variation using a resistive sensor, and external pressures at the wound site; with a loop antenna to wirelessly transfer data using IEEE 802.15.4. The reusable part comprised wireless electronics. Carbon ink was used on paper substrate to realize the bottom electrode, with the top electrode and sensor electronics printed on Kapton film using silver nanoparticle ink. A standard bandage was sandwiched between top and bottom electrodes and wearability and bending stability were confirmed along with sensing performance.

2.8. Toxicity or chemical detection: organophosphate compounds

Mishra et al. (2017) proposed a disposable glove-based sensing platform to detect toxic chemicals, including Organophosphate (OP) compounds, which could be used for chemical warfare and environmental applications. The sensor was flexible, low cost, scalable, and wearable. Two-dimensional stretching was achieved using customized ink and serpentine microstructures. The proposed biocatalytic process performed swipe sampling and electrochemical reactions on different fingers. Enzymes were immobilized on the index finger, and the thumb was used to collect nerve agent residues. OP residues were fingertip sampled and transferred to the thumb (collector) with adhesion ensured by a carbon disk printed on the thumb tip. The thumb was joined with the sensing (index) finger to complete the electrochemical reaction. A conductive semisolid gel matrix (OPH) completed the electrochemical reaction, providing stretch and 50% mechanical strain. A stretchable Ag/AgCl ink was formed by mixing Ercon Ag and AgCl ink with Ecoflex, mixed with PS-PI-PS in xylene to prepare stretchable carbon ink for screen printing. Various target surfaces were contaminated using OP compounds (methyl paraoxon and methyl parathion) to evaluate biosensor performance. Electrochemical reaction data were wirelessly transmitted to a smartphone.

3. Discussion

Table 1 compares salient WWB features. Sensitivity, response time, and dynamic range are of particular interest.

1. Higher sensitivity and dynamic range are essential for practical WWB utilization.
2. Wearable wireless biosensors should provide quick response time for POC and ambulatory settings. Long wear times for frequent or continuous monitoring over a day is practically feasible only if the WWB is ultrathin, light weight, compliance to human skin and equipped with wireless technology (powering and data transmission).

Table 1
Various relevant parameters for noninvasive wearable wireless biosensors discussed in this article.

Indicator	Position	Sensing modality	[a]Sensitivity (LOD)	Bend tests	Substrate/active material	[b]Response time and dynamic range	Reference
Sweat metabolites, electrolytes, skin temperature	Wristband, headband	Potentiometric	Glucose: 2.35 nAμM^{-1} Lactate: 220 nAmM^{-1}	60 cycles	PET	< 1 min [Na+]: 20–120 mM [K+]: 2–16 mM Glucose: 0–200 μM Lactate: 2–30 mM	Gao et al. (2016)
Sweat lactate, potassium	Eyeglasses	Potentiometric, amperometric	Lactate LOD: 0.39 mM	N/A	PET	30 s [K+]: 0.1–100 mM	Sempionatto et al. (2017)
Sweat metabolites, electrolytes, lactate, pH	Forearm	Hybrid colorimetric/ biofuel cell system		Yes	PDMS microfluidics, Pyralux	N/A N/A	Bandodkar et al. (2019)
Sweat lactate, ECG	Chest	Amperometric	Lactate: 96 nA/mM	N/A	Transparent polyester	N/A Lactate: 0–28 mM	Imani et al. (2016)
Glucose within tears, intraocular pressure	Contact lens	Graphene FET with hybrid S/D	Glucose in buffer and tears: 1 μM	5000 stretch cycle for 25% uniaxial tensile strain	PET, PDMS Graphene + Ag NW	5 h Glucose: 0.001–10 mM	Kim et al. (2017) a,b
pH	Sweating area	Strain	11.13 ± 5.8 mV/pH	500 cycles for 30% strain	Polyimide film	< 8 s pH: 5–9	Dang et al. (2018)
Sweat sodium	Arm	Strain	63.75 mV/log$_{10}$[Na$^+$]	180° repeated bending strain	Tattoo base paper, PET	10 s [Na+]: 0.1–10 mM	Bandodkar et al. (2014)
Sweat alcohol	Arm	Iontophoresis, amperometric	N/A	90° bending	Tattoo base paper	7.5 min Ethanol: 0–36 mM	Kim et al. (2016)
Lactate	Sweating area	Organic electrochemical transistor	1 mM	N/A	Kapton	Several minutes Lactate: 0.25–10 mM	Currano et al. (2018)
Lactate	Skin mounted	Amperometric	262 nA mM^{-1} cm^{-2} Fabrication	8 mm bending for 10000 cycles	PET Ag NP	< 2 s Lactate: 1–25 mM	Abrar et al. (2016)
Uric acid through saliva	Mouthguard	Amperometric	2.32 μA/mM	N/A	PET	2 min Uric acid: 0–1 mM	Kim et al. (2015)
ECG, HR	Chest	Strain	N/A	N/A	Polyimide	N/A N/A	Lee et al. (2018)
Pulse rate	Wrist, neck	Pressure	0.025 MPa	10^6 cycles	PEN P(VDF-TrFE) Polyimide	0.2 s N/A	Sekine et al. (2018)
Respiration rate, volume monitoring	Chest	Strain	N/A	2000 cycles with 156–226% strain	Ecoflex	N/A N/A	Chu et al. (2019)
Vocal cord movements	Skin worn	Strain	N/A	10000 stretch cycles under 30% strain	PDMS, GaInSn	N/A N/A	Jeong et al. (2017)
Cerebrospinal shunt flow monitoring	Skin worn	Pressure	80%	Yes	Ecoflex	6 min N/A	Krishnan et al. (2018)

Notes: PET: Polyethylene terephthalate, LOD: limit of detection, FET: Field effect transistor, PEN: polyethylene naphthalate, P(VDF-TrFE): Ferroelectric polymer, LOD: limit of detection.
[a] LOD is used for sensitivity if the latter was not provided in the indicated article.
[b] Response time and dynamic range are listed in that order in the column.

We briefly discuss performance of WWBs discussed above. Lactate concentration in human sweat typically ranges from 0 to 25 mM and varies slightly with metabolic activities (Green et al., 2004). Gao et al. (2016), Imani et al. (2016), and Abrar et al. (2016) reported lactate concentration dynamic range as 2–30, 0–28, and 1–25 mM respectively. Considering typical lactate range in human sweat, Gao et al. (2016), Imani et al. (2016), and Abrar et al. (2016) met the dynamic range requirement. Currano et al. (2018) reported 0.25–10 mM dynamic range for lactate, achieving significantly improved LOD compared to several other proposed devices. The achieved dynamic range by Dang et al. (2018) and Kim et al. (2015) for pH and AU level also met the corresponding ranges for human blood. Kim et al. (2017a,b) reported excellent glucose concentration LOD = 1 μM from tears. Dang et al. (2018), Bandodkar et al. (2014), and Sempionatto et al. (2017) also reported excellent response times (8, 10, and 30 s, respectively).

The cerebrospinal shunt flow monitoring device by Krishnan et al. (2018) achieve 80% sensitivity, whereas conventional techniques such as X-ray, CT, MRI, and RSPS achieve 4–26%, 54–80%, 40–62.8%, and 47–65%, respectively.

4. Challenges and prospects

Wearable biosensing paradigms change continuously and quickly with continuous advancements in materials, fabrication technologies, and wireless power. Recently, significant developments include epidermal biosensors to monitor cerebrospinal shunt flow, ECG, respiration rate, and some leading-edge multifunctional wearables. POC testing, self-health management, and patient remote monitoring are broad and high impact concepts enabled by WWBs. Four metrics are typically considered to validate wearable biosensor development: fast response time, selectivity, reproducibility, and wide dynamic range (Sempionatto et al., 2017). Appropriate routes for further research and development can be developed based on better understanding of current WWB status and challenges.

Skin barrier for noninvasive sensing. It remains a significant challenge to access biofluids beneath the skin during normal activity, since the skin is a complex matrix of layers and acts as an effective information barrier. Transdermal drug delivery has developed several methods to disrupt the epidermal barrier, but new techniques are also required, including mechanical methods, e.g. microneedles; tape stripping; or enhancing chemical permeability. Only invasive techniques provide access to analyte concentrations in blood and interstitial

fluid. Chemical impedance remains very high for all noninvasive methods; hence efficacy remains challenging. The skin can also contaminate target analytes during sample collection. For example, bacteria reside on human skin in abundance, consuming glucose and producing cellular waste products. Chemical contamination could be reduced for noninvasive sweat sensing applications, e.g. an occluding layer of petroleum jelly/oil could minimize sweat contacting the epidermis (Heikenfeld et al., 2018).

Long-term reproducibility. Discomfort and irritation from long term wearing are considerable and important challenges, including biocompatibility, skin-compatible form factor, durability after washing, mechanical bending, and light weight (Liu et al., 2018). For example, an ideal WWB should capture analyte concentration over long continuous measurement periods. However, active material layers may decay or dissolve with continuous analyte addition on the sensor surface. Applying an effective outer protective layer could prevent enzyme solutions and anionic polymers from percolation (Abrar et al., 2016).

4.1. Elasticity issues

- **Flexible substrate noncompliance with human skin.** Human skin comprises a complex matrix with highly anisotropic composition, producing strongly nonlinear stress-strain curves. Young's modulus of elasticity for human skin also varies enormously with age, hydration, and target site. Silicone elastomers, e.g. PDMS, have been extensively used in biochemical sensing devices, but it is significantly stiffer than human skin, which can lead to delamination (Heikenfeld et al., 2018). Choi et al. (2018) showed that these platforms cannot be stretched because they are insufficiently elastic, with relatively high modulus and hence cannot accommodate large strain deformations. Consequently, limited options exist for integration with body regions parts that present complex contours and/or significant skin deformation during natural motions. Significant mismatch between intrinsically stretchable skin and non-stretchable skin mechanics leads to stress at the interfaces, and subsequent delamination, particularly during intense exercise. Zhao et al. (2018) fabricated a wavy structure on a Kirigami based bandage (PDMS/Ecoflex) with enhanced human skin adhesion (knee) compared with conventional film (continuous).
- **Active material mechanical deformation.** Conductive patterns are realized using nanoparticle based metallic inks utilizing screen and/or inkjet printing techniques. Bending issues not only limit design freedom, but also complicate retaining connectivity and adequate conductivity after mechanical deformation. Human joints have high stretching pressure (~55%), whereas conventional flexible sensors LOD is very low. Tang et al. (2018) proposed a 0.04 mm thick paper based flexible patch antenna sensor using multiple graphene layers with conductivity = 10^6 S/m. High temperature treatment (2000 °C) helped achieve in-planar orientation and hence high conductivity and low sheet resistance graphene.

4.2. Sweat dependence

- **Sweat-generation dependence.** Sweat-based activity monitoring requires an intense exercising/exertion or exposure to hot environment to generate a certain volume of sweating for a WBB to be responsive. Maybe users facing certain health risks, acute conditions and those in elderly age cannot meet these requirements. This necessitates to invent new sensing modalities and WBBs to be able to perform more autonomously. Alternatively, iontophoresis techniques exist which are independent of abovementioned sweat-generation requirements (Choi et al., 2018).
- **Sweat rate dependency issues.** Many wearable biosensors have been proposed to extract physiologically relevant parameters from sweat. However, several fail to provide true correlation between analyte levels in sweat and blood, which must not include Na + and lactate (Hauke et al., 2018). Thus, sweat generation must be steady and sensor performance should be independent of sweat rate. Low sweat rate, sample evaporation, and utilizing freshest sweat have been mentioned as considerable challenges in sweat sensing WBBs (Bariya et al., 2018).

4.3. Selectivity challenges

Some biosensors have not demonstrated selectivity, which is the most important qualification parameter for practical applications. Human sweat contains several ions, and metabolites which in itself is a challenge. In case they could be simultaneously loaded to the wearable biosensors, biosensor should have capability to differentiate between target and non-target fluids (Liu et al., 2018). In addition, a risk of external contamination in human sweat for instance through cosmetics on human skin, also exist.

4.4. Multisensing platform

Currently, single parameter detection facilitated by a wearable biosensor is insufficient. Wearing two or more biosensors is cost-inefficient as well as inconvenient for wearer. Simultaneous monitoring of multiple analytes using a single-chip wearable biosensor should be further investigated. Generally, the device size inevitably increases with increasing functionality. Therefore, multisensing skin compatible platform with small form factor are increasingly explored.

4.5. Inadequate sensitivity to detect trace ions/elements

Wearable biosensors sensitivity should be strongly enhanced to identify biomarkers found in trace amounts in the human body (Salim and Lim, 2018a). For example, 4 ng/ml concentration of prostate-specific antigen in blood can indicate prostate cancer, leading doctors to suggest biopsy tests (Bhalla et al., 2016).

4.6. Durability in fully operational mode

Bending tests are conducted to validate the stretchability of these WBBs. The results of bending tests remained successful and the WBBs were found to be intact. It may not be a true depiction of durability. However, reproducibility of these WBBs in fully operational mode after conducting a number of measurements for a period of time is not fairly demonstrated in the articles.

4.7. Powering of miniature sensors

Suitable energy sources in skin compatible form factors is another challenge. Direct contact of the reagent layer with biofluids is essential for wearables biosensors, whereas the associated electronics circuitry must be sealed from the aqueous environment (Bandodkar and Wang, 2014). WWBs should provide uninterrupted response of readout circuits. Energy harvested from sunlight, body movement, sweat, or friction could be utilized as alternatives to conventional batteries in coming future. Multiple sources of energy in a single biosensor could also be considered to switch between various options which can facilitate in continuous supply of power to circuitry (Bandodkar et al., 2016).

4.8. Cost and calibration challenges

Wearable wireless biosensors should be self-calibrated so that users do not need to perform time-consuming tasks, such as pre-sampling or conditioning; and the sensors should be mass producible at low cost. For commercialization the cost of sensing device should be as low as possible (Salim and Lim, 2018b).

4.9. Privacy/cyber security issues

Accessibility of the data (personal health information) on wireless links may prone to certain risks. For instance, if information is hacked and the physiological status of a healthy person is falsified as a patient or vice versa, in either case it may put person's life at risk.

4.10. Need of DNA-based sensors

Despite various novel sensing platform developments, WWBs sensing modalities remain limited to sweat, tears, and saliva to monitor electrolytes, glucose, lactate, saliva for uric acid level, ECG, heart rate or wrist flexion, finger/vocal card movement. More advanced WWBs, such as DNA detection and analysis remain to be developed (Turner, 2013). We anticipate DNA biosensors utilizing buccal mucosa as a diagnostic tool for genetic disorder or carcinoma buccal mucosa (oral cancer) are likely to be developed in the next few years.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Ahmed Salim: Conceptualization, Investigation, Resources, Data curation, Writing - original draft. **Sungjoon Lim:** Writing - review & editing, Supervision, Project administration, Funding acquisition.

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Appendix A. Supplementary data

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