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Wearable Biosensors for Body Computing

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The challenges of growing and aging populations combined with limited clinical resources have created huge demand for wearable and portable healthcare devices. Research advances in wearable biosensors have made it easier to achieve reliable noninvasive monitoring of health and body status. In this review, recent progress in the development of body computing systems for personalized healthcare is presented, with key considerations and case studies. Critical form factors for wearable sensors, their materials, structures, power sources, modes of data communication, and the types of information they can extract from the body are summarized. Statistically meaningful data analysis considerations, including using cohort and longitudinal correlation studies, are reviewed to understand how raw sensor signals can provide actionable information on the state of the body. This informs discussions on how collected sensor data can be used for personalized and even preventative care, such as by guiding closed-loop medical interventions. Finally, outstanding challenges for making wearable sensor systems reliable, practical, and ubiquitous are considered in order to disrupt traditional medical paradigms with personalized and precision care.

1. Introduction

Traditional modes of monitoring physical and physiological health and fitness rely on hospital-based care with in-person consultations, lag times between testing and assessment, expensive equipment, and discrete analysis.[1–3] Not only is this inefficient and costly, it fails to allow careful monitoring of evolving health conditions, including sudden changes in physiological state such as hypoglycemic events or dehydration during exercise.[4,5] In response, a novel landscape of decentralized healthcare relying on a network of wearable devices and wireless communication promises to allow for immediate, continuous, and personalized health monitoring.[6,7] Systems in this new landscape of body computing for personalized healthcare use sensors that interface with the body to extract physical and physiological signals in real time (**Figure 1**). These sensors connect to phone apps and cloud platforms to consolidate raw signals and parse them into actionable health information using big data analytics and artificial intelligence. Beyond revealing health status to the user, these platforms further connect individuals with virtual health care providers that can determine interventions and therapies based on sensor output.[8,9] Alternately, sensors connect directly to closed-loop on-body systems that can deliver precision drug doses or recommend behavioral changes (such as gait adjustment in physiotherapy).[10] By expanding the body information available to us and using it to modulate the ways in which we conduct ourselves and interact with our environments, these personalized healthcare systems augment the ways in which we can understand and control body function, and potentially enable seamless integration of individuals with personalized medical care anywhere and at any time.[6,11]

In this review, we highlight key considerations and case studies that capture recent progress in the development of body computing systems for personalized healthcare. We focus on wearable sensors, including their materials, structures, power sources, modes of data communication, and the types of information they can extract from the body. We next review schemes of data collection and analysis, including using cohort and longitudinal correlation studies, to understand how raw sensor signals can give us actionable information on the state of the body. We discuss how this data can be used for personalized and even preventative care, such as by guiding closed-loop medical intervention. We summarize by considering outstanding challenges for wearable sensor systems that must be addressed to make body computing for personalized healthcare a safer and more reliable component of emerging healthcare.

2. Body Surfaces and Secretions for In Situ Analysis

The location at which a wearable sensor is envisioned to interface with the body, and the type of biofluid or biosignal that it measures, informs sensor design.[12] Before reviewing structural and material considerations, we first review key body

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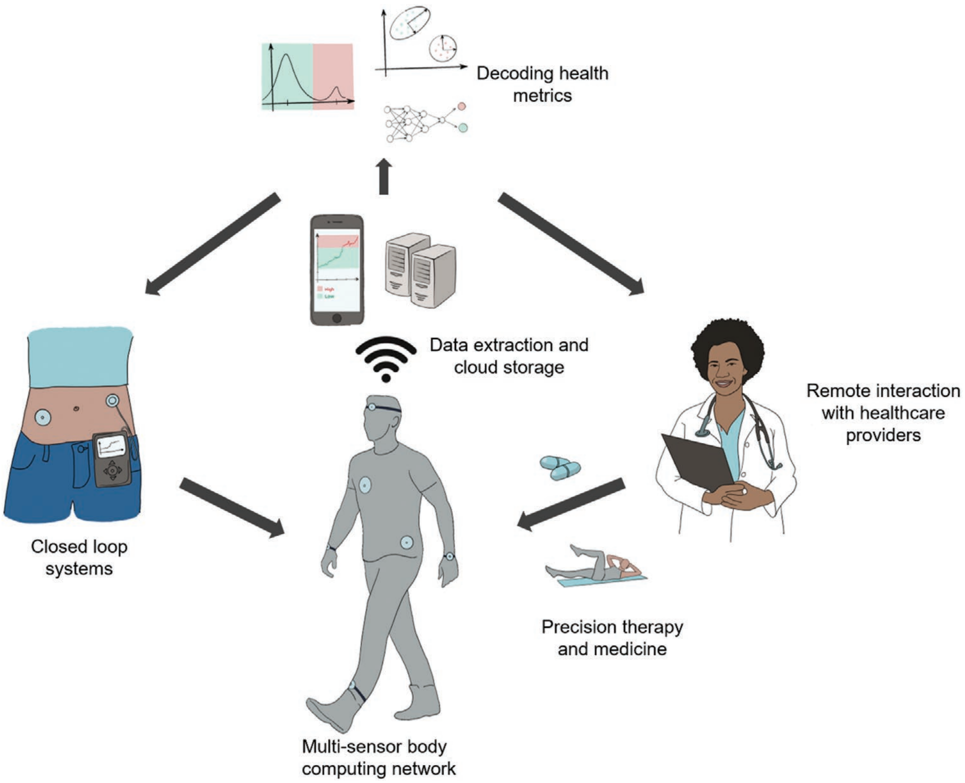

Figure 1. Schematic illustration of body computing for personalized health monitoring. Wearable biosystems for body computing use sensors to monitor physical and physiological status. Using big data analytics and artificial intelligence, the extracted signals are transmitted to mobile and cloud platforms, and processed into actionable health information. These biosensing platforms enable seamless integration of individuals with personalized medical care either via closed-loop systems or virtual healthcare providers.

surfaces and secretions that wearable sensors can target for noninvasive monitoring, and what broad information they can offer about the state of the body and its interactions with the environment.

2.1. Skin

The skin is the largest body organ and offers abundant discreet and convenient areas for wearable sensor attachment. Sensors attached conformally to skin can probe physical body indicators including heart rate, blood oxygenation, and electrophysiological signals from neuron activity. Skin also mediates the body's interaction with its environment through complex sensations of touch and temperature, allowing other skin sensors to detect temperature, pressure, and movement. These various physical signs can indicate the health of the body and guide personalized rehabilitation therapies.

2.2. Skin Secretions—Sweat, Interstitial Fluid (IF), and Wound Exudate

Biofluids secreted through skin have rich molecular compositions, allowing skin-attached sensors to directly yet noninvasively access biomarkers that could reflect the deeper chemical and physiological state of the body.[13] Skin-mediated secretions include sweat, IF, and wound exudate, or secretions produced by the body at sites of tissue damage during healing. Sweat can be accessed at distributed body sites by actively elevating body temperature through exercise or thermal treatment, or can be passively and continuously accessed at small volumes and low secretion rates as the body finely manages thermoregulation.[14,15] Sweat can also be locally induced through iontophoretic chemical stimulation. Sweat contains high concentrations of ions, metabolites, and xenobiotics as well as lower concentrations of proteins, hormones, and DNA, making it an attractive biofluid for noninvasive health monitoring.[6,16] Interstitial fluid is another chemically rich biofluid that can be accessed through the skin. IF is found surrounding cells in the extracellular spaces and contains many of the same molecules found in blood, including salts, acids, sugars, and other small molecules, but notably lacking red blood cells.[17] Components of IF are filtered in from blood at levels that correlate closely with blood levels for several molecules including glucose, making IF an attractive surrogate for traditional blood-based diagnostics and monitoring.[18] IF can be locally, noninvasively withdrawn through the skin via reverse iontophoresis, a process of electro-osmotic fluid and biomarker retrieval. A third biofluid accessed on the skin is wound exudate, liquids secreted by wounds as a part of the reparative process, and which can maintain hydration and act as a barrier to bacteria and debris.[19] Wound exudate contains proteins, nutrients, electrolytes, enzymes, and inflammatory components, with a composition that evolves over the stages of healing. Real-time monitoring of indicators including pH, acids, and inflammation proteins can therefore be used to track the progression of healing or identify the onset of infections.

2.3. Saliva

Saliva is easy to access on-demand and has a composition that varies with body health and state, making it attractive for noninvasive health monitoring.[20] Typical salivary production rates can exceed 1 L a day, and levels of metabolites, enzymes, hormones, and proteins can alter in response to exercise, dietary intake, chronic diseases like diabetes and pancreatitis, stress and depression, and cancer.[21,22] Salivary flow rate can also be indicative, as it changes based on hydration, medications, and circadian rhythms and can further modulate biomarker concentrations. However, saliva is prone to contamination, so care is needed to ensure that the analytes being sampled are representative of secretions from salivary glands and not residual food or drink.

2.4. Tears

Tears are attractive for continuous health monitoring due to their on-demand and abundant supply, with tears typically being generated at rates of over 1 μL min^{-1}.[23] Tear composition includes salts, proteins, and lipids, with key biomarkers including glucose and cholesterol showing promising correlations with blood concentrations. Levels of nutrients, dissolved gases, growth factors, and pH are narrowly regulated in healthy individuals but can deviate for patients with health conditions, underscoring tears' diagnostic potential.[24] Tear composition can directly signify ocular disease such as dry eye, in which certain protein levels increase. Autonomic conditions can affect rates of tear production, as can various drug therapies.

2.5. Breath

Breath is an attractive medium for noninvasive health monitoring as it can be safely accessed without needing direct body contact and is thus convenient to monitor across diverse populations, from newborns to athletes to patients. Breath sensors need not adhere to strict requirements for biocompatibility and flexibility that other wearable sensors must follow, and can thus seamlessly take advantage of existing electronics manufacturing materials and technologies. Exhaled breath has thousands of components that arise from the lungs and nasal cavities or have systemic origins in blood.[25] Constituent gases including volatile organic compounds (VOCs), ammonia, and nitric oxide among others can indicate diseases like jaundice, asthma, diabetes, and lung cancer, while breathing patterns can also reflect respiratory conditions like sleep apnea.

3. Sensor Materials and Platform Considerations

Materials, structures, and form factors are important considerations in the design of wearable computing systems. Sensor components in contact with the body must be biocompatible and use separation or encapsulation techniques to protect against contamination.[26] Material breathability and resistance to water damage should be considered when sensors are intended for biofluid sampling. Electrodes that sit flush against the skin must be conductive but not rigid—even as the underlying body site moves and contorts, they must retain integrity under strain and have appropriately robust architectures. Sensor size can depend on available volumes of the biofluid being accessed, on the timescale of sensor operation on body, and on comfort and wearability. Sensors that serve medical purposes might adopt discrete form factors like patches, while those for athletic purposes can utilize more conspicuous wristband or headband formats. These are some of the consideration that inform the design and development of body computing and wearable sensors. Below we highlight some broad solutions to these and other constraints.

3.1. Materials and Structures for Flexible and Wearable Electronics

Wearable electronics for body computing must typically be able to withstand the strains of on-body wear. This is particularly the case for sensors that are conformally attached to soft body sites like skin. In order to maintain their integrity as the underlying surface deforms, sensors can be made out of soft, stretchable materials, incorporate thin layers or nanostructures of traditionally rigid materials to impart flexibility, or utilize strain engineered architectures to effectively decrease the overall device stiffness.[27,28] We review these material and structural choices in more details.

3.1.1. Flexible and Stretchable Materials

Polymers are intrinsically bendable and a common choice for flexible electronics. They can serve as substrate and packaging materials or be engineered into stretchable conductors that are the basis of wearable electronic devices including skin-like sensors, wearable energy harvesters, and soft actuators.[29,30] Polymers that are attractive as sensor substrates include polydimethylsiloxane (PDMS), polyethylene terephthalate (PET), and polyimide (PI), while conductive polymers like polyaniline (PANI), polypyrrole (PPY), and poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS) can be used as electrode and transducer materials. Composites that encapsulate metals within polymeric networks marry conductivity with stretchability (**Figure 2**A).[31] Conductive inks that combine polymer binders with conductive nanoparticles can be printed to produce planar, flexible electrodes and interconnects, or permeated through other materials to impart conductivity (Figure 2B).[32] Hydrogels use crosslinked networks of hydrophilic polymers to maintain their structure even as they swell to accommodate large volumes of water, offer an important consideration for devices operating

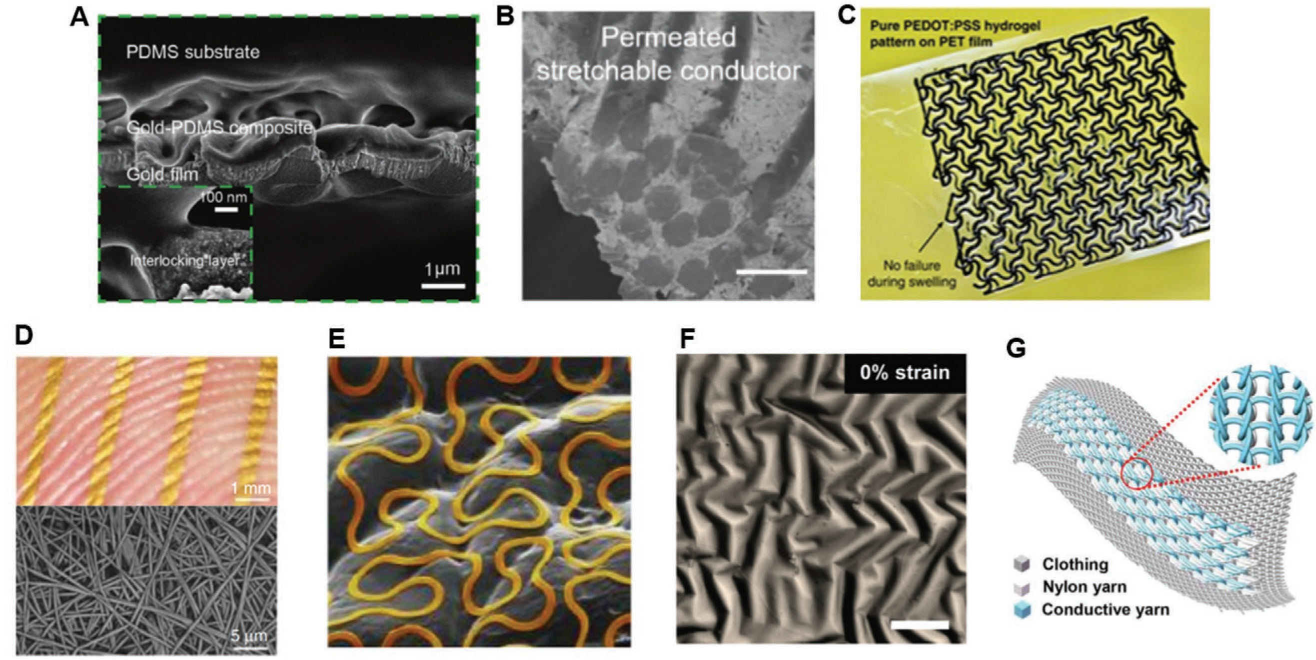

Figure 2. Materials and structures for conformal sensors. A) Metal–polymer composite for flexible and conductive films. Reproduced with permission.[31] Copyright 2019, Wiley-VCH GmbH. B) Textile-permeable conductive ink for flexible e-fabrics. Reproduced with permission.[32] Copyright 2017, Wiley-VCH GmbH. C) Conductive and stretchable PEDOT:PSS polymer networks with tunable swelling. Reproduced with permission.[35] Copyright 2019, Nature Publishing Group. D) Metallic nanowire network for highly skin-conformal electrodes. Reproduced with permission.[42] Copyright 2017, Nature Publishing Group. E) Serpentine, strain engineered electrode structure. Reproduced with permission.[44] Copyright 2014, Nature Publishing Group. F) Out-of-plane wrinkles of conductive film accommodates strain. Reproduced with permission.[45] Copyright 2015, The Royal Society of Chemistry. G) Interwoven conductive yarn for stretchable smart textiles. Reproduced with permission.[46] Copyright 2020, American Association for the Advancement of Science (AAAS).

in wet physiological environments.[33] These materials are attractive for wearable sensor applications as their stiffness moduli can be tuned to match that of skin or tissue, allowing for sustained contact.[34] Hydrogels can be made conductive by directly using conducting polymers (Figure 2C) or by embedding conductive materials into the polymer network, allowing their use in flexible electronics.[35,36] Significant research has been recently conducted on achieving high conductivity in hydrogels and other polymers through tuning of dopants and fabrication conditions.[37]

3.1.2. Flexible Nanostructures

Nanomaterials and high-aspect ratio nanostructures that can be patterned into films or arrays can impart flexibility for electronic components, allowing conductive materials that are rigid in their bulk forms to be adapted for body-interfacing applications.[38–39] We have seen that incorporating 0D nanoparticles into elastomeric matrices can produce composite materials and inks for flexible printed components.[40] 1D and 2D structures including metal nanowires, thin metallic sheets, carbon nanotubes, and graphene are commonly used as conductive electrode materials for elastic, large-area sensor networks.[41] For example, meshes of gold nanowires can be directly laminated onto skin to produce flexible conductive traces for direct, on-body electronics (Figure 2D).[42] However, the biocompatibility of nanomaterials is still unclear, so care must be taken to ensure they do not leach into the body from sensing materials and electronics.

3.1.3. Strain Engineered Structures

Apart from using flexible materials, another approach to ensuring electrodes maintain structure and performance under strain is by designing their layout such that large strains in the underlying substrate translate to small local strains within the electrodes.[43] This can be done by patterning interconnects in serpentine or mesh structures, having electrodes wave out of the sensor plane with intermittent tethering points, creating prewrinkled conductive films, or using interwoven meshes of conductive threads (Figure 2E–G).[44–46] These morphologies can rotate or buckle to accommodate deformations, reducing overall stiffness and enabling more stretchable and flexible electronic structures.

3.2. Sensor Form Factors

Wearable systems' form factors are informed by the type of biosignals being monitored. For example, sensors that detect electrical pulses beneath the skin must be structured for highly conformal skin contact. Sensors that wick up skin secretions must securely seal against skin to prevent evaporation and leakage, while salivary sensors must be able to sit unobtrusively

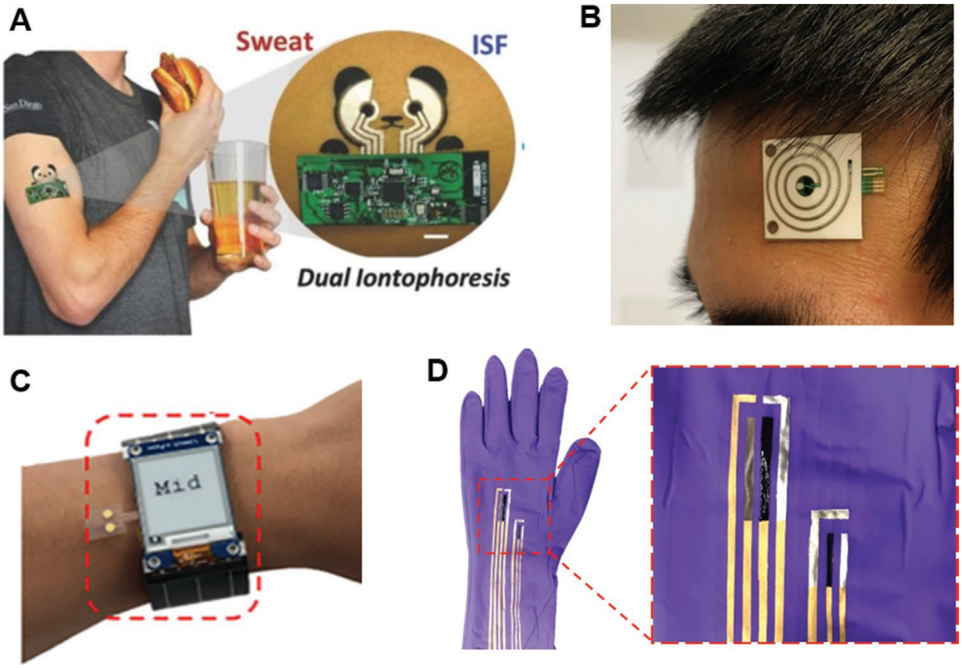

Figure 3. Form factors for skin-conformal sensors. A) Tattoo with electrochemical sensors for sweat and IF analysis. Reproduced with permission.[49] Copyright 2018, Wiley-VCH GmbH. B) Patch with microfluidic and sensors for sweat sensing. Reproduced with permission.[51] Copyright 2019, AAAS. C) Wrist strap sensor for glucose. Reproduced with permission.[54] Copyright 2019, American Chemical Society. D) Glove. Reproduced with permission.[14] Copyright 2020, AAAS.

in the mouth. A wide variety of form factors can be adopted to satisfy these constraints. Wearable systems can be configured as tattoos, patches, bands, clothing, and accessories to effectively measure secretions and signals while being comfortable to wear.

3.2.1. Skin-Interfaced Sensors

Sensors that interface with skin for monitoring physical vital signs or biomarkers in skin secretions have unique flexibility and stretchability requirements to accommodate deformations of the curvilinear skin surface on which they are attached.[47,48] Specifically, sensors must be mechanically robust, lie flush with the skin surface to access dermal electrical signals or secretions, and deform along with skin curvature and strains. These constraints guide sensor design including sensor attachment mechanisms and overall form factor (**Figure 3**).

i. Tattoos

Sweat and interstitial fluid sensors must lie close to the skin surface to capture freshly secreted fluid with minimal evaporation. One approach involves patterning sensing electrodes onto adhesives that can be directly applied to the skin as temporary tattoos (Figure 3A). Kim et al. patterned electrodes and contacts for iontophoresis and reverse iontophoresis onto temporary tattoo transfer paper, enabling simultaneous sweat and IF induction and sensing in a consolidated device.[49] Wang et al. used a cut-and-paste method to tattoo gold electrodes, less than 2 µm thick, in an open-mesh structure that reduces artefacts from motion and trapped sweat compared to thicker, large-area tattoos, enabling more accurate skin temperature, hydration, and pulse sensing.[50] Tattoo sensors can be affixed at diverse body sites and are suitably discreet for medical monitoring applications. However, one challenge is ensuring noise-free connection between the highly thin and conformal electrode layer and associated circuitry for signal extraction. Further, some sensor measurements may be prone to evaporation artefacts as tattoos do not encapsulate biofluids like sweat before measurement.

ii. Patches and bands

Skin-affixed wearables like sweat sensors can also be packaged as patches mounted with medical-grade adhesives (Figure 3B).[51] This form factor allows diverse sensor placement and versatile incorporation of microfluidics to guide sweat flow and limit evaporation. To maintain close skin-to-sensor contact, patches can be made with soft materials like PDMS, with thin and flexible plastic substrates, or intentionally made of flexible but non-stretchable materials to ensure integrity of fluidic channels and preserve a tight seal against the skin surface to prevent sweat leakage.[51,52] For athletic applications, sweat sensors can alternately be packaged smart wristbands and headbands that constitute a convenient and familiar form factor for sports.[53] Zhao et al. developed a sweat sensing watch with a digital display for direct and simple readout of biomarker levels (Figure 3C).[54] An added benefit of this strap-on form factor is that sensor adhesives will not delaminate from high sweat secretion volumes.

iii. Textiles and clothing

Sensors for biomarker measurements and vital signs can further be integrated into textiles and clothing. “Smart” garments have been successfully commercialized for contactless payments and simple measurement of body fitness metrics, but there are growing opportunities to incorporate more advanced physical and chemical sensors. Bariya et al. functionalized sweat sensors within nitrile gloves that take advantage of high sweat gland densities on the hands and limited evaporation through the nitrile to accumulate large volumes of natural, passively produced thermoregulatory sweat without needing active sweat induction (Figure 3D).[14] Conductive interconnects can be woven into fabric to form temperature sensors, detect electrical activity related to the heart and brain, or have shape sensitivity for motion detection.[55] Liu et al. developed conductive stretchable fabrics to infer joint rotation from skin deformation, advancing over existing motion capture systems for athletic and physical rehabilitation applications.[56] Piezoelectric and photovoltaic elements can also be incorporated into smart textiles for integrated energy harvesting from body motion or ambient light to power sensor processes.

3.2.2. Other Mountable Sensors

i. Mouthpieces

Wearable sensors that do not interface to deformable body sites like skin have less stringent flexibility requirements, though other constraints may be relevant. Salivary sensors can have sensing layers and wireless transmission electronics integrated into rigid mouthguards (**Figure** 4A), as Kim et al. demonstrated for salivary uric acid (UA) measurement and monitoring of hyperuricemia drug therapy.[57] Sensors can alternatively be packaged in more flexible, planar orientations to directly affix to the teeth, as Tseng et al. did for dielectric sensors that distinguish between different consumed foods.[58] In both cases, sensor components must be well encapsulated to prevent contamination and degradation, a particular challenge in the humid and bacteria-prone environment of the mouth.

ii. Contact lenses

Tears can be accessed noninvasively with flexible sensors partially contacting the eye or directly integrated into contact lenses. Flexible electrodes and transmission components like antennae can be fabricated directly onto the convex contact lens surface (Figure 4B).[59] However, this form factor has not been demonstrated for on-body use in human subjects, and outstanding challenges include ensuring sensor components are transparent and produce negligible local heating during operation.

iii. Other accessories

Other body computing systems involve packaging sensors into form factors including glasses, shoes, and other accessories. Ota et al. presented a continuous core temperature tracker that has sensing and transmission components integrated into an earpiece, a structure with renewed promise for detecting infectious virus symptoms (Figure 4C).[60] Sweat sensors can be functionalized onto the skin-contacting surfaces of glasses' nose-bridge pads, potentially allowing sweat analysis in elderly populations as this site is naturally prone to sweating (Figure 4D).[61] Sensors for bending and force detection can be integrated into shoes for gait estimation, with important applications in rehabilitation and outpatient safety (Figure 4E).[62,63] Güder et al. integrated paper-based humidity sensors into masks to analyze respiration, a simple form factor that could be extended to support breath composition analysis (Figure 4F).[64] Smart electronics integrated into accessories have also seen commercial success beyond research prototyping. Fitness tracking bracelets and smart watches are ubiquitous, and newer products include L'Oreal's nail sticker that tracks UV exposure.

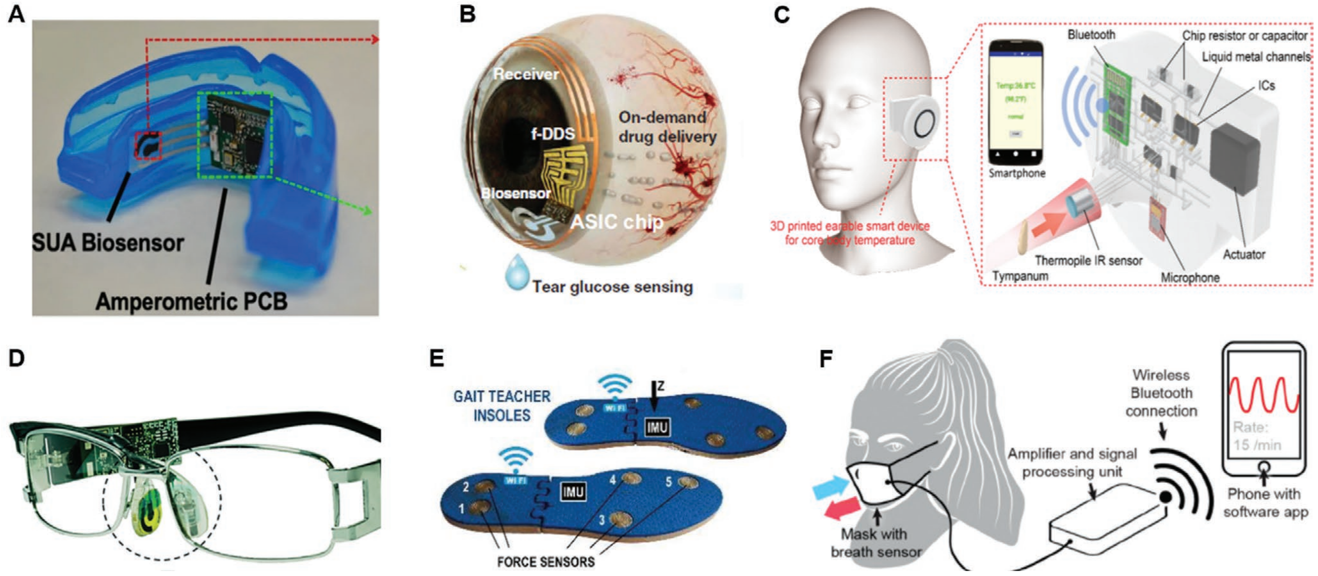

Figure 4. Form factors for mountable and accessory sensors. A) Mouthpiece. Reproduced with permission.[57] Copyright 2015, Elsevier. B) Contact lens. Reproduced with permission.[59] Copyright 2020, AAAS. C) Earpiece. Reproduced with permission.[60] Copyright 2017, American Chemical Society. D) Glasses. Reproduced with permission.[61] Copyright 2017, The Royal Society of Chemistry. E) Shoes insoles. Reproduced with permission.[63] Copyright 2019, EasyChair. F) Mask. Reproduced with permission.[64] Copyright 2016, Wiley-VCH GmbH.

Overall, accessories offer abundant form factors for interfacing wearable electronics with the body in convenient and nonintrusive ways.

4. Biosignals for Wearable Sensing

Wearable sensors have been developed to target a vast library of physical and chemical indicators, providing comprehensive avenues of insight into the body's cardiac, respiratory, and endocrine health among other body functions. Here, we detail some representative sensors and the biosignals they extract to demonstrate the broad ways in which body computing systems can noninvasively probe the state of the body.

4.1. Physical Sensors

Physical sensors measure quantities like temperature, displacement, pressure, strain, and electrical activity. Wearable physical sensors can monitor biosignals including heart activity, neuronal activity, and signals originating from motion and contact to provide information of the body and its interaction with the environment.[65] We now present a few examples for these classes of physical biosensors, and consider how material, structural, and sensing scheme choices are made for better biosignal access.

Lee et al. developed a wearable patch for electrocardiogram (ECG) and heart rate readings (**Figure** 5A).[66] The patch is thin and flexible for intimate coupling with skin, advancing over traditional bulky heart monitoring instruments as well as the noisy skin interfaces of first-generation wearable ECGs. Polyurethane encapsulation protects the device from water ingress, allowing continuous measurement for hours with wireless transmission of waveforms to a smartphone for data processing and interpretation. This long operating time is important as a user's personal ECG signature must be learnt in order to make heart rate estimates.

Li et al. used ultrathin optoelectronic circuits attached to skin like tattoos for wireless determination of arterial blood pressure without requiring an inflatable cuff (Figure 5B).[67] The patch attaches to skin with gentle van der Waals interactions, eliminating skin irritation to enable continuous measurement over long periods of wear. Noninvasive detection of arterial waveforms relies on a stable optical path between the light sources, photodetectors, and others components involved in the measurement process, but this is made difficult by the deformability of skin. Postprocessing of the extracted signals is required to compensate for this effect.

For electrophysiological monitoring, Tian et al. prepared large-area skin-like sheets with stretchable serpentine electrodes that can be conformally shaped over different areas of the body while accommodating strains introduced through motion (Figure 5C).[68] This work introduces manufacturing methods for large-area sensors, techniques for mounting sheets with removable polymer supports to maintain conformal skin contact over large areas, and materials to ensure a breathable and nonirritating interface. The resulting skin-like sensor sheets can be attached to the cranium to map brain signals with electroencephalography (EEG), interfaced with magnetic resonance imaging (MRI), or attached to sites of limb amputation for prosthetics control.

To assess stress, Yoon et al. made a stamp-sized patch for multimodal detection of skin temperature, conductance, and arterial pulsewaves (Figure 5D).[69] Heart rate variability and temperature are expected to increase under stress, as is skin conductance due to an increase in sweat gland activity. Stacked layers minimize the device footprint to reduce skin irritation, and flexible piezoelectric materials are combined with open-structured supports to enhance the device's overall flexibility.

Along with the electrical and pulsewave biosignals monitored by the above devices, physical sensors can be made to target motion and pressure to decode the body's interactions with its environment.[70]Monitoring tactile sensations and interactions has numerous applications in health monitoring, robotics, and virtual reality (VR). Gao et al. reported a microfluidic pressure sensor embedded in a wristband format that uses liquid-metal-based

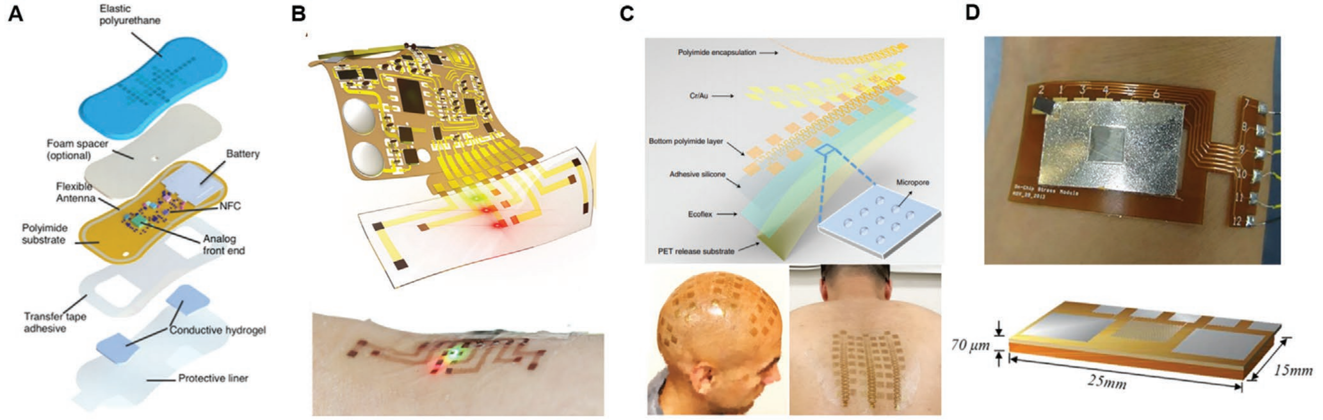

Figure 5. Wearable physical sensors for electrical biosignals. A) Wearable cardiac sensor for monitoring ECG and heart rate signals in remote and ambulatory settings. Reproduced with permission.[66] Copyright 2018, Nature Publishing Group. B) Optoelectronic sensor with suppression of motion artefacts for continuous blood pressure monitoring. Reproduced with permission.[67] Copyright 2020, Oxford University Press. C) Large-area, MRI-compatible electrode networks for simultaneous EEG and EMG monitoring. Reproduced with permission.[68] Copyright 2019, Nature Publishing Group. D) Stress monitoring patch with skin conductance, temperature, and arterial pulse-wave sensing. Reproduced with permission.[69] Copyright 2017, Wiley-VCH GmbH.

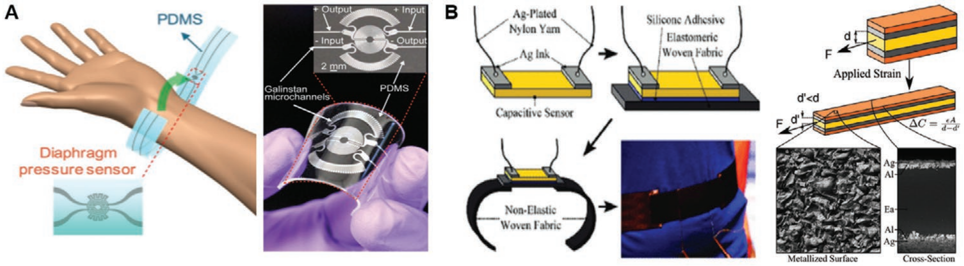

Figure 6. Wearable physical sensors for motion and pressure sensing. A) Microfluidic diaphragm sensor for sensing motion and pressure. Reproduced with permission.[70] Copyright 2017, Wiley-VCH GmbH. B) Strain sensors based on microstructured electrodes for capacitive monitoring of arm motion and respiration. Reproduced with permission.[71] Copyright 2017, Wiley-VCH GmbH.

sensors capable of withstanding extreme strains to provide tactile feedback upon touching and holding objects (**Figure 6**A).[70] Unlike other devices that seek to minimize the impact of skin deformation on signal integrity, this device relies on skin deformation and corresponding perturbations of the sensor's elastomeric substrate to detect fine changes in pressure.

Motion sensing can be realized using capacitive strain sensors as demonstrated by Atalay et al., who integrated sensors into fabric sleeves and belts for on-body monitoring of respiration and movement (Figure 6B).[71] Prestrained elastomeric sheets are subjected to microstructural surface texturing to enhance stretchability of overlaying metal electrodes for a wider crack-free strain range. In general, this method of incorporating microstructures and stretchable substrates is a common approach to making wearable physical sensors more durable for on-body wear.

4.2. Chemical Sensors

In contrast to physical sensors, chemical sensors transduce chemical concentrations, redox potentials, and reaction rates. Wearable chemical sensors monitor the body's physiological state by detecting concentrations of analytes including metabolites, ions, heavy metals, hormones, acids, and xenobiotics across biofluids like sweat, saliva, and tears. Electrochemical, colorimetric, and optical schemes can be used for concentration analysis. Sensors can also track biofluid secretion rates, which modulate secreted analyte concentrations and are important for interpreting concentration measurements. We next survey some representative examples of wearable chemical sensors.

Electrochemical sensors for concentration analysis are attractive to their simple detection schemes and low detection limits, and many sensors for sweat-based physiological monitoring use electrochemical sensors for biomarker quantification. Bandodkar et al. developed a sweat sensing patch with microfluidics to isolate sweat from the skin surface and prevent biofouling (**Figure 7**A).[72] Near-field communication (NFC)-powered electrochemical sensing of metabolites is combined with colorimetric sensing of ions and visual monitoring of sweat rate for continuous monitoring that is battery-free. Yang et al. presented an electrochemical patch for detecting sweat uric

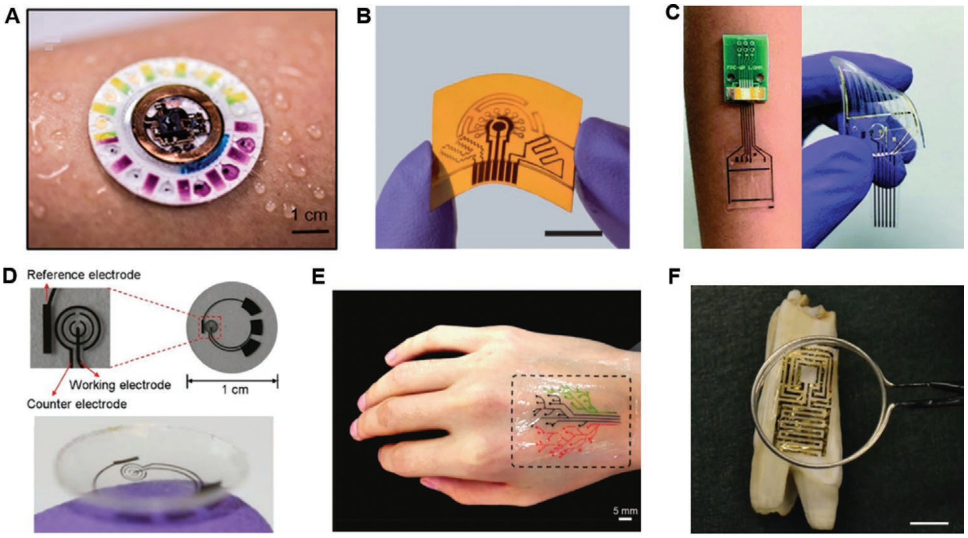

Figure 7. Wearable chemical sensors for biomarker sensing. A) Colorimetric ions and sweat rate sensing. Reproduced with permission.[72] Copyright 2019, AAAS. B) Sweat uric acid and tyrosine sensing patch. Reproduced with permission.[73] Copyright 2019, Nature Publishing Group. C) Multimodal monitoring of sweat ions and secretion rate. Reproduced with permission.[74] Copyright 2019, The Royal Society of Chemistry. D) Tear-based lactate sensing contact lens. Reproduced with permission.[75] Copyright 2011, Elsevier. E) Optical fluoresce sensor for inflammatory biomarkers. Reproduced with permission.[76] Copyright 2017, Wiley-VCH GmbH. F) Antimicrobial peptide (AMP) recognition molecules for bacteria detection. Reproduced with permission.[77] Copyright 2012, Nature Publishing Group.

acid and tyrosine (Tyr) , which they found can be indicative of high protein diets and patients with gout (Figure 7B).[73] Laser engraving is used to rapidly pattern electrodes for chemical and physical indicators, and microfluidics are again used to entrap sweat and minimize evaporation. Yuan et al. developed a third microfluidic sweat sensor for multimodal monitoring of sweat ions and generation rate (Figure 7C).[74] To ensure flexibility, electrodes are patterned on thin PET beneath soft PDMS fluidics. By using a discrete sensing scheme with interdigitated electrodes beneath the fluidic channel that respond to the advancing sweat fluid front, highly selective sweat rate sensing is achieved. This is an advancement on previous autonomous sweat rate sensors that show interference from sweat conductivity. Such a device could be used in athletic applications for hydration monitoring, or to study electrolyte imbalances in the elderly, which can cause decreased attention, impaired gait, and higher risks of falling.

Electrochemical sensors can be applied beyond analyzing skin secretions like sweat. Thomas et al. made an electrochemical lactate sensor in a contact lens form factor for monitoring tear-based excretion of lactate from the body (Figure 7D).[75] A permselective Nafion encapsulation layer inhibits interference from many components of the rich tear, while a nonfunctionalized, control electrode is used to subtract away background signals from other interferents. In future, radio components could be integrated for wireless signal transmission from the contact lens.

Optical methods of chemical detection include fluorescing sensor components. Liu et al. used 3D printing of hydrogels containing programed bacterial cells to produce stimuli-responsive structures on wearable patches (Figure 7E).[76] These patches can be made into sensors that fluoresce in response to signaling chemicals. The hydrogels are printed over skin-like elastomeric sheets that maintain conformal body contact without delamination of the "living" tattoo, and could in future be programmed toward other chemicals including inflammatory biomarkers.

Electrical methods of chemical sensing include using electrodes functionalized with biorecognition elements and detecting impedance changes that arise when those elements interact with their target molecule. Mannoor et al. developed a tooth tattoo comprising of graphene functionalized with antimicrobial peptide (AMP) recognition molecules to detect bacteria in saliva and tooth enamel (Figure 7F).[77] Due to their elasticity and biodegradability, silk films are used as supporting substrates to conformally transfer the graphene tattoo onto the tooth. Coil antennas are patterned on the tattoo for wireless extraction of the impedance signal. This detection scheme, enabled by passive interaction of sensor and target, requires no external power input and is well suited for autonomous wearable sensing.

5. Bioenergy for Self-Powered Sensors

In most cases, wearable electronics for applications in personal healthcare and continuous body monitoring are powered by batteries.[53,78–80] However, external power sources fail to enable autonomous operation for extended times without requiring user intervention. Instead, body computing systems can have self-powering capabilities by directly harvesting energy from the environment (e.g., from solar energy and wind power) or from bioenergy naturally released by the body (e.g., from body movement and perspiration).[81,82] Using these clean and abundant energy sources to power wearable sensing devices have attracted increasing research interest.

5.1. Perspiration-Powered Devices

Devices that can harvest bioenergy in noninvasive manner have attracted considerable attention.[82] For example, by utilizing the enzymatic redox reaction of lactate in sweat, electrical flow can form and generate power output collected.[78,83] Such devices are known as biofuel cells (BFCs). Integrated wearable patches with BFCs for self-powered body sensing have been reported in a variety of platforms such as of textile, a self-powered band/watch.[79,84]

The generated electrical current densities are generally proportional to the analyte concentrations in body fluid. Thus, to achieve stable power output, device stability and proper bio-power module designs are critical challenges to be addressed.[82] Gao and co-workers reported a fully perspiration-powered electronic skin with biosensing capability as shown in **Figure 8**A.[85] It is worth mentioning that the combination of nanomaterials in different dimensionals contributes to a record breaking power intensity. The stable and efficient self-power capability enables the monitoring of critical metabolic analytes and Bluetooth wireless data transmission to the user interface. Such platforms can also serve as a human–machine interface.

Apart from noninvasive health monitoring, a self-powered skin electrochromic timer with automatic activation of microneedle array for drug dose management was developed by Nishizawa and co-workers, as shown in Figure 8B.[86] The electrochromic timer consists of an enzyme (fructose dehydrogenase) modified carbon electrode, which generates current flow with the existence of fructose on skin. The displayed color depth is a result of redox reaction charges, indicating the time lapse. When in contact with skin, transdermal current flow can activate the integrated porous microneedle array integrated with the electrochromic timer. The as-developed skin patches are expected to be further explored as a platform for drug dosing and wound healing monitoring in fields of healthcare/medical and cosmetics.

5.2. Body Heat Dissipation

Human body heat dissipation varies quite significantly across the body and can be largely influenced by the surrounding. For instance, under sedentary status and room temperature, the general heat flow is around 1–10 mW cm^{-2}, while it can be as high as 10–20 mW cm^{-2} on the wrist.[87] Thermoelectric devices can convert continually released body heat into reliable power output for functional devices as a result of the temperature difference between the human body and the surrounding. This heat flow with temperature gradient, generates a voltage by the Seebeck effect. However, the temperature difference on the human body and environment is normally quite limited, thus

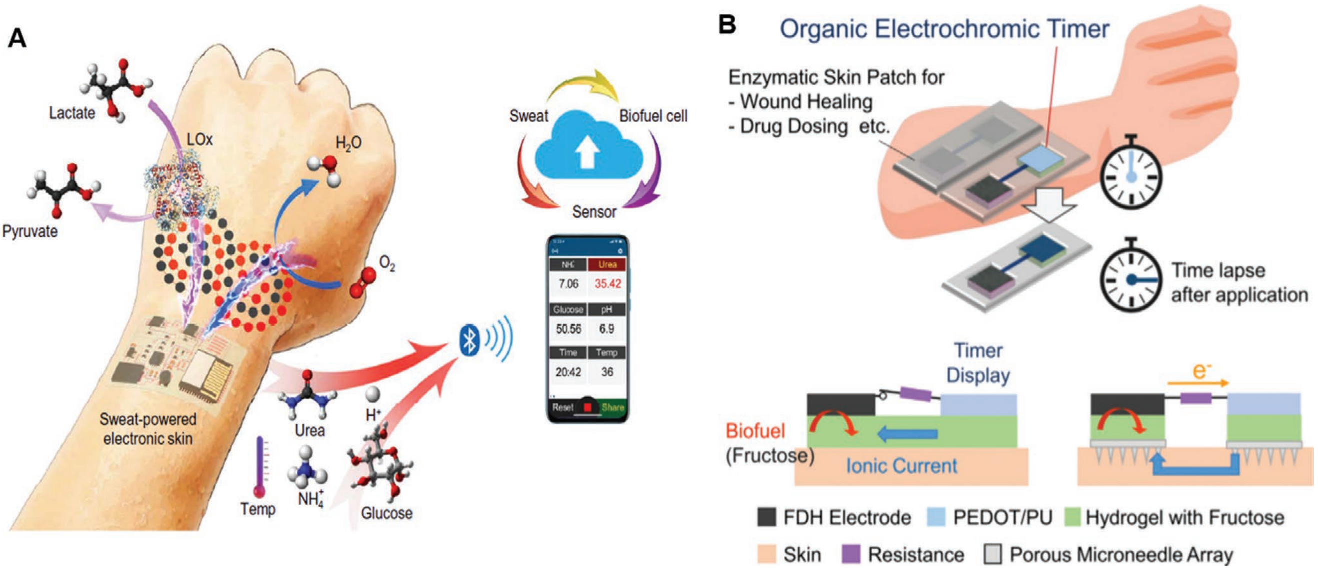

Figure 8. Biofuel cells for self-powered sensors. A) A flexible and fully perspiration-powered integrated electronic skin for multiplexed metabolic sensing. Reproduced with permission.[85] Copyright 2020, AAAS. B) A self-powered skin electrochromic timer with automatic activation of microneedle array for drug dose management. Reproduced with permission.[86] Copyright 2018, Elsevier.

it introduces high thermal resistance and poses challenges to stable and sufficient power output for wearable applications.[88] One of the common practices to achieve low thermal resistance is to integrate a heat sink to the cooler side of the device. Metal heat sinks with large surface area have shown capability to achieve sufficient heat exchange, while its heavy weighted and inflexible nature limits its integration into wearable devices.

Recent advances in flexible and high thermal conductive heat absorbers and new types of heat sinks seek to address the limitation of low power efficiency and the rigid and bulky nature of traditional thermoelectric generators, so as to facilitate utilizing body heat to power up wearable sensors. Superabsorbent polymers with intrinsic flexibility and can be engineered with large surface area morphologies, which facilitate heat exchange, have shown to be a promising alternative to metal. For instance, Cho and co-workers reported using sodium polyacrylate as a superabsorbent polymer. Such long-chained molecule provides superior properties to anchor water molecules. The thermoelectric generators with such polymer-based flexible heat sink realized an impressive output power density of 38 μW cm^{-2} as compared with 8 μW cm^{-2} with a metal heat sink[88] **Figure 9**A shows a skin-attachable thin film thermoelectric generator as power supply for continuous physiological monitoring and motions tracking with a pressure sensor.[89] The combination of thermal conductive polymer films for heat absorption and hydrogel heat sink performs a high output voltage. The 3D network hydrogels with large water content allow quick water evaporation and heat dissipation factor. The device showed a remarkable enhancement up to 92% compared to those without hydrogel heat sinks. These values are among the records of

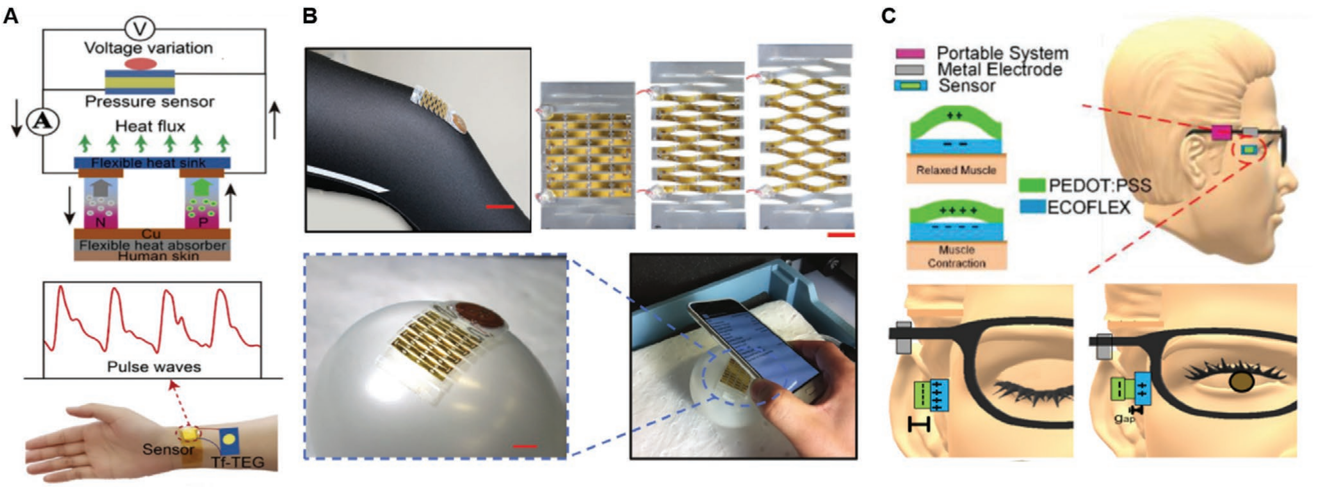

Figure 9. Body generated energy for self-powered sensors. A) Thermoelectricity. Reproduced with permission.[89] Copyright 2020, Elsevier. B) Piezoelectricity. Reproduced with permission.[91] Copyright 2019, Wiley-VCH GmbH. C) Triboelectricity. Reproduced with permission.[92] Copyright 2020, Elsevier.

flexible skin-attached thermoelectric generators. For self-powered sensing systems utilizing the body released heat, it is critical to ensure that the sensing performance is independent of the temperature gradient, so as to achieve reliable biosignals.

5.3. Motion Energy

Mechanical energy generated via vibration or friction can also be collected. Piezoelectric nanogenerator (PENGs) and triboelectric nanogenerators (TENGs) has aroused tremendous research interest.[81,90] These devices can generate proportional signals to the mechanical deformation. When arranged in arrays, they can function as both multipixel motion sensors and high-power output generators, which has promising applications in human–machine interface.

Several types of semiconducting materials, such as zinc oxide, have been utilized for motion energy devices. Normally, the resulted AC signals needs to be converted to DC output via a bridge rectifier. Figure 9B shows a kirigami inspired self-powered piezoelectric sensor for wearable body motion tracking.[91] This device is composed of a stretchable self-powered piezoelectric sensor, and a flexible NFC module interface for wireless data transmission. Interestingly, kirigami-based architecture significantly enhanced the stretchability, and realized a conformable and compliant interface to human skin.

On the other hand, TENGs utilize electrostatic phenomenon when friction force is applied. There are mainly two devices configurations for sliding and contact operation modes respectively operation. For instance, potential difference can be generated eletrostatically when there is triboelectric interaction between the two components. Figure 9C demonstrates a wearable eye blinks tracker based on triboelectric sensor. The power output of the motion sensor can also support the wireless near-field communication. It allows further integration with human–machine interface to achieve intelligent eye motion control applications.[92]

5.4. Simultaneous Self-Powered Sensing Platforms

Simultaneous sensing platform with infinite self-powered capability is highly desirable for wearable and portable devices. The integration of biosensors into wearable electronics to achieve comprehensive body computing will require proper matching of power supply modes and power management for sensor functionality, data extraction, and decoding. The power supply module is expected to provide sufficient power density for biosensing as well as the functionality of other supporting components. For instance, the triboelectric voltage output normally exceed the capacity upper limit of most electronics, thus it cannot be directly connected to the system as power generator. In this regard, it is of significance to develop power management solutions and design the corresponding circuits, so as to realize stable functionality of self-powered systems even in harsh environment.

Hybrid energy harvester for multitypes of energy have attracted research interest due to their capability to achieve higher power harvesting and conversion efficiency, as well as reduced risks of power cutoff. Recently, Zhang and co-workers reported a flexible energy harvester for simultaneously solar and mechanical energy collection, as shown in **Figure 10**A.[93] A flexible organic solar cell on the outward surface and a TENG attached to skin were integrated via a common electrode. The hybrid energy harvester is controlled by a power management module to utilize the large photovoltaic current and the high triboelectric voltage output. The converted electricity realized fast charging and superior performance compared to single harvester module.

Another strategy to eliminate environmental constraints for a self-powered system is to integrate energy harvesting and storage devices to ensure continuous power supply, such as BFC-supercapacitor, nanogenerator-supercapacitor.[94,95] A variety of self-powered systems in both rigid and flexible platforms have been designed and fabricated successfully. The system functional mechanism can be illustrated by the schematic diagram as shown in Figure 10B.[96] The reported self-powered wristband utilizing solar energy to support gas sensing applications, and photocharging supercapacitors for backup energy storage. In such integrated systems, the collected energy can either directly drive the active devices, or can be stored and released controlled by designed circuits.

These advances of self-powered sensor systems can inspire the research efforts on wearable devices for next-generation

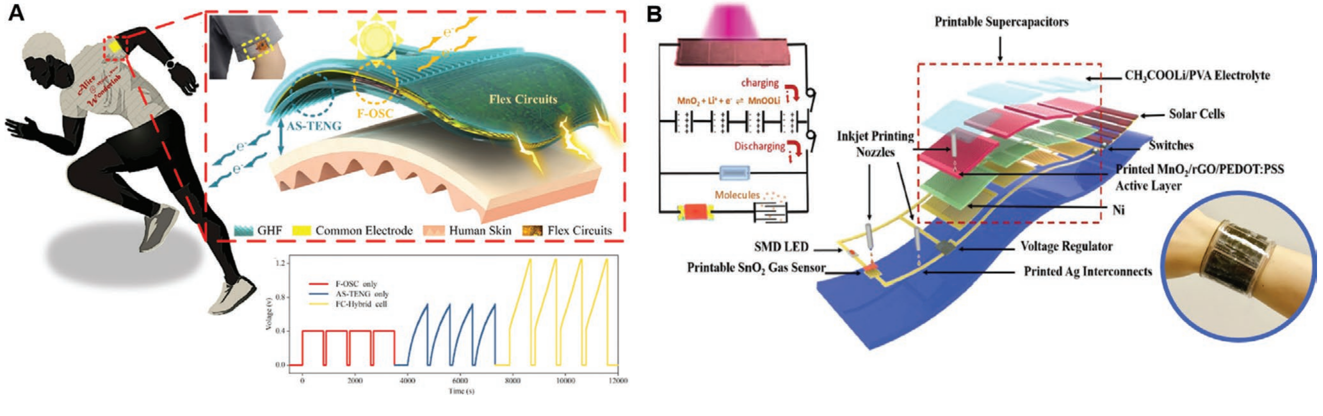

Figure 10. Power Management for self-powered sensors. A) Hybrid energy harvesting system for simultaneously harvesting both solar and mechanical energy. Reproduced with permission.[93] Copyright 2019, Elsevier. B) Integration of energy conversion and storage devices. Reproduced with permission.[96] Copyright 2018, Wiley-VCH GmbH.

intelligent body computing, especially for long term tracking personalized healthcare, biomedical monitor applications.[97] It is worth noting that apart from improving the power management capability and stability in flexible and stretchable platforms, special research efforts are required for rational and friendly wearable designs on the skin interaction interface to eliminate mechanical interference.

6. Biosignals Extraction

Wireless networks have largely benefited our daily life. This also contributes to the advances in biosensing data extraction to efficient and intelligent fashion without relying on costly and bulky laboratory tools. To facilitate accurate noninvasive biosensing, especially with minimum biofluids that can either be quickly evaporated or be easily contaminated during sample collection and transfer, delicate research efforts have been emphasized on real time data assessment.[98]

6.1. In Situ Analysis and Display

In situ and straightforward biosignal assessment is preferable for patient-friendly wearable tracking devices, as it provides a simple and clear feedback. Especially for users without clinical background, it is unnecessary to display the exact numeric results of the biosensing on wearable devices. Thus, colorimetric quantitative readout with convenient comparison with calibration markers appears to be one of the most convenient schemes. As shown in **Figure 11**A, Rogers and co-workers used enzymatic reaction to trigger colorimetric response to realize biomarkers concentrations in situ readout.[98] The as-developed wearable sweat sensing patch consists of microfluidics for sweat collection and colorimetric assays to allow quantitative assessment of perspiration rate and biomarkers. With optimized cocktail composition and standard fabrication of enzymatic colorimetric assays, these sensors provide the attractive high reproducibility and calibration-free properties. However, such colorimetric sensor readout schemes possess limitations for sensitivity and continuous monitoring.

To enable continuous health monitoring, Zhao et al. developed a smart watch that incorporating self-power capability, noninvasive biosensing, signal analysis, and data display in an integrated platform (Figure 11B).[54] The flexible photovoltaic panel and rechargeable aqueous batteries served as self-power watchband. Noninvasive glucose monitoring is achieved via sweat sensing, and the biosignals are in situ processed and display on the customer designed watch panel with embedded microcontroller and low power display. Innovative design on these wearable platforms with operational convenience are expected for daily body computing.

6.2. Wireless Data Transmission

The breakthrough in industries and interdisciplinary research fields, such as Internet of things (IoTs), has revolutionized communications into an intelligent and wireless connected network. Nowadays, transmission of data or information with a high speed to other devices can be widely achieved over a distance by using electromagnetic waves like radio frequencies, infrared, satellite, etc., without requiring wires, cables, or any other electrical conductors.[99] There are well developed wireless communication technologies, such as NFC, Bluetooth, Zigbee, and Wi-Fi. Device network arrangement and power consumption will be the main considerations for integration with biosensing devices. In general, Bluetooth, NFC, and Zigbee offer low power consumption for portable devices. Bluetooth provides the best power per bit requirement and suitable for continuous data communication. On the other hand, NFC is ideal for "touch to action" data extraction. However, Zigbee is not compatible with mobile operating systems currently, limiting its applications in wearable biosensing data extraction. Although WiFi is relatively power hungry, it provides efficient information and data transmission to cloud storage for big data analysis. Therefore, Bluetooth and NFC are preferable for sensor to mobile devices wireless communication, and become most commonly used wireless communication schemes for body computing applications.

NFC enables contactless power delivery and data transmission across a distance of a few centimeters based on

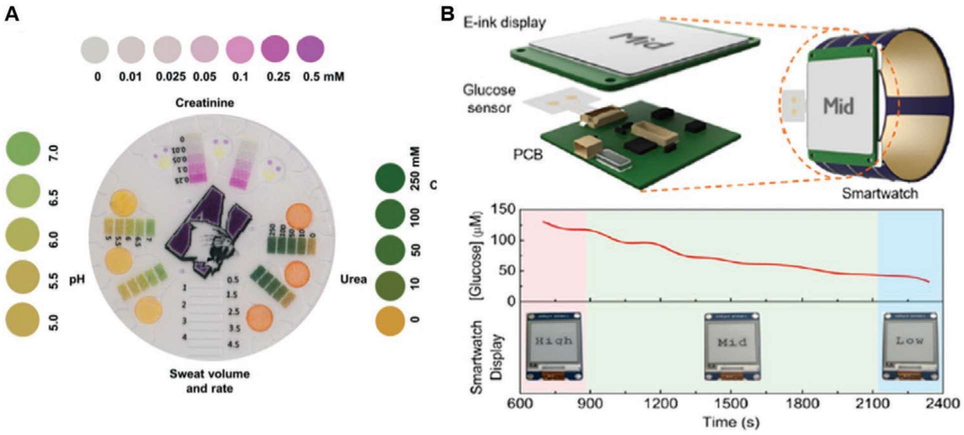

Figure 11. In situ biosensing data display. A) Colorimetric readout. Reproduced with permission.[98] Copyright 2019, The Royal Society of Chemistry. B) E-ink alarm signals display. Reproduced with permission.[54] Copyright 2019, American Chemical Society.

Figure 12. Wireless data transmission. A) NFC. Reproduced with permission.[72] Copyright 2019, AAAS. B) Bluetooth. Reproduced with permission.[101] Copyright 2018, American Chemical Society.

radio frequency identification (RFID). It provides advantages including low power consumption, lightweight, and small device volume. It has been well developed for contactless payments, access control, and interactive tags, and compatible with most of the mobile devices, such as smartphones. Therefore, it appears to be an attractive biosignals readout scheme. **Figure 12**A shows that a reversible magnetic NFC module can be conveniently attached to a disposable colorimetric biosensing platform.[72] Such NFC electronics have also been embedded in wearable sensors in a variety of formats, including disposable band, etc. It enables robust data extraction and instant analysis with mobile app, which provides more accurate readout of the biosensing results.

Compared with NFC that data transmission is only possible when the sender and receiving antennas are located in direct proximity with each other, Bluetooth as an ultralow-power consumption technology uses radio waves in a range of several tens of meters to communicate between paired devices.[100] However, only two devices can be connected at the same time. Thus, proper designs of device identification and pairing functionality are required so as to allow one receiving end node to extract biosignals from multisensing devices for comprehensive body computing. As shown in Figure 12B, a wearable microfluidic patch was integrated with a custom-developed printed circuit board, which realized signal processing and Bluetooth communication with a smartphone that preloaded with a custom designed user interface.[101] The real time and wireless data transmission strategy enables dynamic sweat secretion analysis and provides easy read-out profiles for sweat rates and biomarkers, without interference from users' physical movements.

Overall, the development of wireless sensors network will no doubt pave the way for intelligent body computing and its implementation in fields of point-of-care and remote diagnostics. However, it is essential to establish standards on data privacy and security when using wireless data and information communication.

7. Decoding Biosignals with Correlation Studies

The physiological significance of certain biosignals are well established, particularly for physical indicators and for traditionally examined biofluids like blood. For example, high or erratic heart rate is a red flag for cardiovascular disease, fevers can indicate infection, and blood creatinine is a starting point for assessing kidney function. Wearable sensors that target these biosignals therefore have clear diagnostic utility. However, recent technological developments have made many other biosignals newly accessible in ways that traditional, off-body measurement systems with large sample requirements could not. These older tools precluded fundamental studies into the physiological significance of biosignals extracted from noninvasively accessed biofluids like sweat. With new wearable systems, we can now retrieve vast quantities of biosignal data but still lack an understanding of what they signify about the state of the body.[102] For example, concentrations of sweat ions and metabolites can be tracked continuously over time, but it is unclear exactly how these evolving profiles relate to the body's deeper dynamic physiology. Further, while elevated levels of certain molecules in blood can indicate disease, their corresponding normal versus elevated concentration ranges in sweat are unknown. To establish the value of tracking these biosignals, it is critical to conduct fundamental investigations into their correlations with body state.[51] In a reversal of the typical tool development process, sensors must first be built to accurately detect these biosignals and then deployed in fundamental scientific studies to determine and validate sensor utility.

The fundamental mechanisms of biomarker filtration into biofluids like sweat and tears are poorly understood but thought to be complex. It is possible that many body factors may impact final secreted concentrations.[74] To reverse engineer how measured concentrations relate to body health, it is important to conduct multivariate studies that track the biosignal of interest along with a wealth of other body parameters that could influence the correlations. For example, in studying how sweat glucose relates to blood glucose levels, studies should track not only glucose concentrations but also broader factors that influence sweating and blood-to-sweat filtration, including diet, hydration, hormone levels, stress, and heart rate. Factors that influence sensor responses must also be considered—for example, sweat pH can influence enzyme activity and therefore signal amplitudes of electrochemical glucose sensors, and should be monitored along with sweat glucose to compensate for this effect when developing sweat-to-blood correlations. Multiplexed sensing is thus a key desired property of body computing systems that aim to fundamentally investigate physiology. Aggregating a large amount of data is critical to identifying statistically significant correlations. For this, both longitudinal and large-scale population studies are necessary. Longitudinal studies are important given that body indicators can have complex relationships, so it is possible that correlations between certain biosignals and body state will be highly personalized. How one individual's sweat composition relates to their blood levels may depend on unique characteristics of that person's metabolism and physiology. Establishing personalized biosignal baselines is thus essential for differentiating between normal and concerning biosignal levels for each individual. On the other hand, it is possible for more universal correlations to emerge across individuals, especially when factors that vary person-to-person are taken into account. Conducting large-scale population studies for big data generation can allow broadly applicable correlations to be developed. In this way, more universal cutoffs for healthy versus concerning biosignal levels can be developed for secretions like sweat and tears, similar to traditional blood tests that have universal healthy ranges for many ions, acids, and metabolites. Overall, large-scale, multiparameter population and longitudinal studies will determine how novel biosignals relate to body health, allowing wearable sensor data to be transformed into actionable metrics that can inform behavioral changes, interventions, and therapies.

7.1. Correlation Studies for Sweat Analytics

While sweat sensor technology has matured significantly in the past few years, very few correlations have been robustly established between sweat parameters and body state or health. For foreign compounds absorbed or ingested into the body, such as nicotine by smoking and caffeine by drinking coffee, sweat is often a primary route of excretion and the mere presence of those molecules in sweat can be informative.[103,104] For example, many recreational and performance enhancing drugs emerge in sweat and can be used for doping control, and toxic heavy metals in sweat indicate dangerous environmental exposure.[105] Alcohol is a rare xenobiotic that has been shown to more closely correlate between sweat and blood. Wearable sweat ethanol patches worn for several hours after alcohol intake revealed similar pharmacokinetics across the two biofluid compartments, with the overall sweat alcohol profile lagging that of blood by up to 35 min (**Figure 13**A).[102] However, exact changes in the sweat ethanol sensor signal in response to fixed alcohol bolus varied between trials and subjects. Further data must be collected to determine if sweat alcohol levels correlate universally and 1-to-1 with blood alcohol content (BAC), or to determine correlation fitting coefficients that account for differences in subject metabolism and physiology.

For endogenously produced molecules, preliminary correlations or the lack thereof can provide insight into fundamental mechanisms of sweat filtration. Microfluidic patches that can monitor sweat composition and secretion rate at various body sites have shown that local sweat loss, particularly on the forehead and forearm, potentially correlate with overall body fluid loss as monitored by repeatedly weighing subjects during exercise (Figure 13B).[51,106,107] This finding suggests that continuous sweat rate monitoring with wearable sensors could be used to estimate hydration status and inform athletes when to replenish their fluid and electrolyte reserves to avoid dehydration. In contrast, the same work showed that fasting iontophoretic sweat glucose concentrations do not universally follow blood glucose concentrations across healthy and diabetic cohorts, even when accounting for sweat rate (Figure 13C). Poor correlation suggests that the mechanism of glucose filtration into sweat from blood may be complex and contingent on broader body factors. Longitudinal studies that compare individuals' sweat and blood glucose dynamics have shown similar profiles between fluid compartments, though further correlation studies must be collected to see if quantitative 1-to-1 correlations can be constructed and if multiplexed sensing of sweat glucose along with other noninvasively accessed body indicators has potential for replacing invasive glucose tests.

In blood, the hormone cortisol elevates in response to stress triggers as well as undergoing a diurnal cycle to mobilize energy reserves. Instead of disruptive and stress-inducing blood tests, noninvasive tracking of circulating cortisol levels would be powerful for tracking mental health and the body's regulation and response mechanisms. To determine if this is possible, a wearable cortisol sensor was developed and used in longitudinal and small-scale subject studies to study sweat cortisol patterns (Figure 13D).[108] Sweat levels replicated the circadian rhythm seen in blood and linearly correlated with plasma levels with a Pearson correlation coefficient of 0.87 across aggregated data from eight subjects, suggesting sweat to be a faithful surrogate for blood cortisol testing.

Recently, a wearable sweat sensor was developed to measure and study UA and Tyr, molecules whose blood levels have

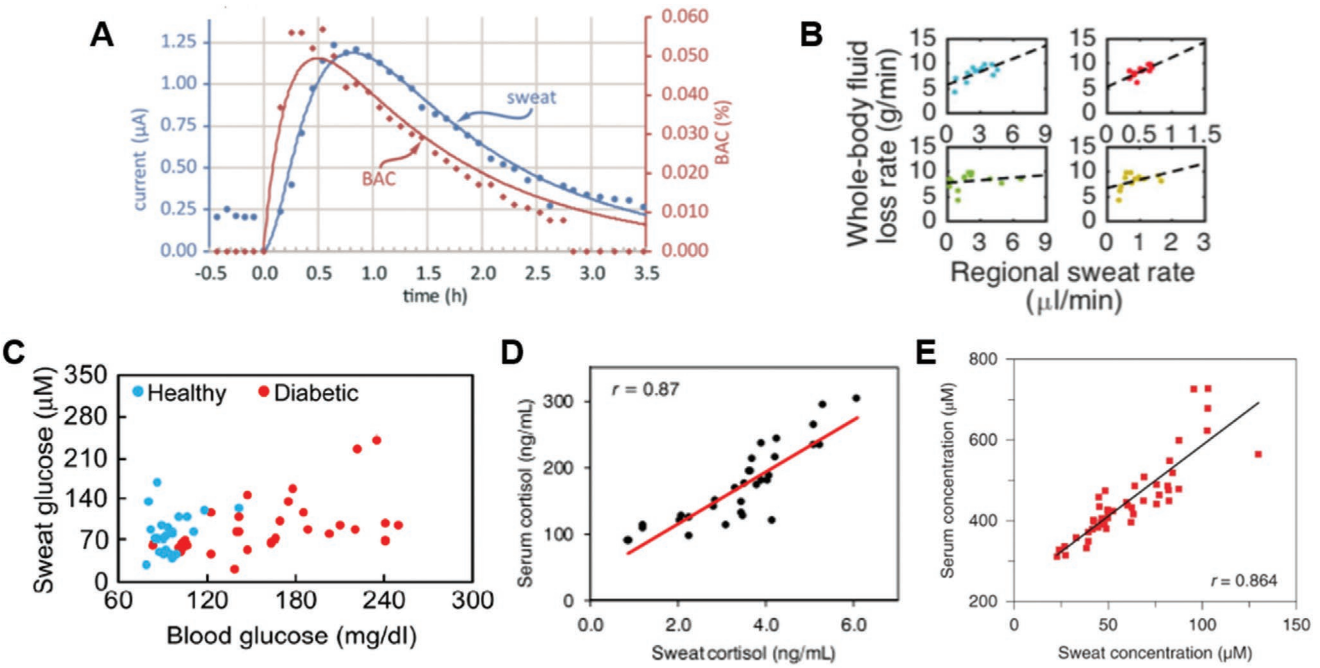

Figure 13. Sweat-based biomarker correlation studies. A) Correlation between sweat ethanol and blood alcohol concentration (BAC) after alcohol intake. Reproduced with permission.[102] Copyright 2018, The Royal Society of Chemistry. B) Correlations between whole-body fluid loss and local sweat secretion rates on the forehead (blue), forearm (red), underarm (green), and back (yellow) during stationary biking. C) Comparison of sweat and blood glucose levels for healthy and diabetic subjects in the fasting state. Reproduced with permission.[51] Copyright 2020, AAAS. D) Linear mapping of sweat and serum cortisol levels. Reproduced with permission.[108] Copyright 2020, Elsevier. E) Correlation between sweat and serum uric acid levels. Reproduced with permission.[73] Copyright 2019, Nature Publishing Group.

been considered for nutritional and metabolic management (Figure 13E).[73] In sweat, UA and Tyr were found to elevate after a high protein diet, with UA levels being further found to correlate with blood concentrations across healthy subjects and gout patients with a correlation coefficient of 0.86 across nearly 50 data points. This and other studies help build a portfolio of applications in which sweat may be valuable in disease diagnosis and management. Expanding these correlations over more data will better define the constraints and capabilities of sweat testing for personalized healthcare.

7.2. Correlation Studies for Other Secretions and Signals

Beyond sweat, other noninvasively accessed biofluids including wound exudate, tears, and saliva have also emerged as candidates for point-of-care health monitoring. By exploiting newly developed wearable technologies including smart contact lenses, sensing mouthguards, and skin-like sensing patches, correlation studies can identify applications for each of these secretions.

The tear proteome has been extensively studied off-body to identify biomarkers for psychological state, pathologies including cancer, and ocular diseases like dry eye.[109] However, in situ measurement by wearable sensors allows real-time, dynamic monitoring of tear composition while reducing evaporation and contamination risks associated with sample storage and transport. Wearable sensors thus offer a fresh opportunity to study the physiological significance of tear biosignals. Sempionatto et al. presented eyeglasses with sensors for alcohol, vitamins, and glucose integrated onto the nose-bridge pad, close to the site of tear secretion.[110] Longitudinal sensor measurements reveal that the tear alcohol profile closely tracks BAC profile, and tear glucose levels rise after meals in a pattern similar to that of blood glucose. Much work is still needed to expand the library of tear compounds detectable by sensors that are safe for direct eye contact. As the technology matures, further correlation studies relating real-time tear biosignals to health state will be possible. Similar to tears, saliva is accessible at high rates and on-demand, allowing it to have a long history of off-body analysis. However, wearable sensors for continuous saliva analysis are creating new opportunities and interest for understanding saliva composition. For example, salivary cortisol levels as monitored with mouthguard sensors have replicated the diurnal hormone variation seen in blood. Wound exudate can also be examined through careful correlations to decode wearable sensor signals. Impedance changes at wound sites have been shown to reflect tissue damage, allowing wearable electrode arrays to indicate sites and stages of pressure ulcers.[111] In addition to decoding chemical sensor signals, multimodal physical sensors that track heart rate, blood oxygen content, and skin temperature were shown to detect the onset of illnesses including Lyme disease.[112]

7.3. Outlook on Correlation Studies for Personalized Healthcare

The development of wearable sensors and systems small enough to enable a density of devices being affixed to the body simultaneously for real-time, near-continuous big data generation has created tremendous new potential for precision health and medicine. The large density and variety of biosignals collected at minimal time intervals can no doubt review the body status change in a more comprehensive manner. For instance, the same drug dosing could perform various effectiveness and metabolism among patients with similar symptoms, which could be attributed to the factors including gender, age, daily diet, and activities. Therefore, population and correlation studies are critical to taking these vast amounts of biosignal data and transforming them into actionable information about the state and dynamics of the body. However, it could be challenging to perform vast amount of data recording and analyzing manually. Thus, the advances in big data analytics and artificial intelligence algorithms can contribute to comprehensive data decoding and provide personalized therapies. Moreover, the biosensing database involving comprehensive calibration factors can be utilized for machine learning so as to further optimize the decoding algorithms and review correlations in a more accurate and intelligent manner. By identifying health conditions as well as their mechanistic underpinnings, these studies are instrumental for making wearable sensor technology truly impactful for personalized health monitoring.

Multiparameter sensing and accumulation of longitudinal biomarker data are key to comprehensively assessing health and detecting deviations from normal baselines that could aid in early disease detection and prevention. While most efforts have focused on sensor development, few studies conducted such longitudinal and population studies to deeply probe sensor data significance. In one work, longitudinal multiomics tracking using wearable systems was used to detect infection and early glucose dysregulation.[112] In another, deep molecular and physiological profiling of a population for up to 8 years was used to learn the healthy baselines of key parameters for different individuals, and then identify pathways associated with metabolic and cardiovascular pathophysiologies.[113] Going forward, it is imperative that more such longitudinal studies are conducted by combining advances in wearable sensors and computational technologies to probe fundamental physiological relations, derive insight into the mechanisms that cause health conditions, and ultimately enable predictive, preventive, precision care.

8. Closed-Loop Body Computing Platforms

Human body relies on a natural and complex closed-loop physiological system to maintain a stable and healthy status. However, it is unavoidable that this intrinsic equilibrium could be disturbed. Thus, there exist research opportunities to develop intelligent and wearable platforms that enable autonomous body intervention with continuous physiological status monitoring.[114] With the advances in a large library of biosensors, integrated user-friendly wearable platforms and intelligent biosignal data processing, closed-loop wearable body computing systems that trigger active functions corresponding to biosensing is one of the promising solution. For next generation closed-loop wearable platforms, reliable biosensors for continuous and minimal invasive monitoring are the core components to provide quantifiable biosignals that indicate the targeted biomarkers levels. With accurate signals decoding, the controller units can deliver command to trigger the actuators to perform tasks, so as to maintain/adjust the target analytes at stable values. The effectiveness is then monitored by the biosensors, which form a closed-loop algorithm. Such wearable closed-loop systems will bridge the gap between biosensing and therapies, which aims at revolutionizing patient care and personalized disease management.

8.1. Drug Delivery

Generally, the functionality of closed-loop drug delivery systems relies on three subsystems, that is, biosensors as analytes trackers, programmable controller as data and demand processor, and actuators for required drug dosing.[114–115] Such closed-loop systems are currently available for anesthesia delivery as well as insulin therapy for diabetes management, based on laboratory tools. Impactful research advances in wearable and portable automated closed-loop drug delivery are expected, with breakthroughs in biomaterials study, flexible sensors, and nanofabrication techniques.

Kim and co-workers reported an integrated system consists of graphene-based multipixel biosensors for sweat glucose noninvasive monitoring and a thermoresponsive microneedle for diabetes therapy on separated skin patches, as shown in **Figure 14**.[116–117] The hybrid patches are connected to a portable electrochemical analyzer. The detection of elevated glucose level will trigger the heater and activate the thermoresponsive microneedles for insulin delivery. However, research in closed-loop automotive drug delivery is still in an early stage. Several challenges including devices long-term stability, therapy effectiveness and reliability, and user safety are to be addressed.

8.2. Rehabilitation

Rehabilitation monitoring is of significance for evaluation of treatment effectiveness, such as postsurgery tracking. Rieger and co-workers integrated epidermal ultrathin sensors for surface electromyography monitoring with data processors to facilitate swallowing therapy after head/neck cancer surgery.[118] Clinical study also suggested potassium monitoring is critical to patients who received cardiac surgery. Development of wearable devices for rehabilitation monitoring will enhance the healthcare quality for patients, enable therapists for remote diagnostics, and eliminate the infection risks for associated with frequent in person clinical visits.

For some diseases/disabilities, rehabilitation therapies are preferable than pharmaceutical and surgical treatments. For instance, joint injuries can lead to deterioration, and pharmaceutical therapies can only alleviate some symptoms, while surgeries usually involve risks. Thus, biomechanical treatments are considered as an effective method for rehabilitation. Conventionally, these biomechanical treatments are conducted with expensive, complex, and space-bound instruments, which limits its implementation in clinical practice. **Figure 15**A shows a wearable biofeedback system using inertial sensors for motion

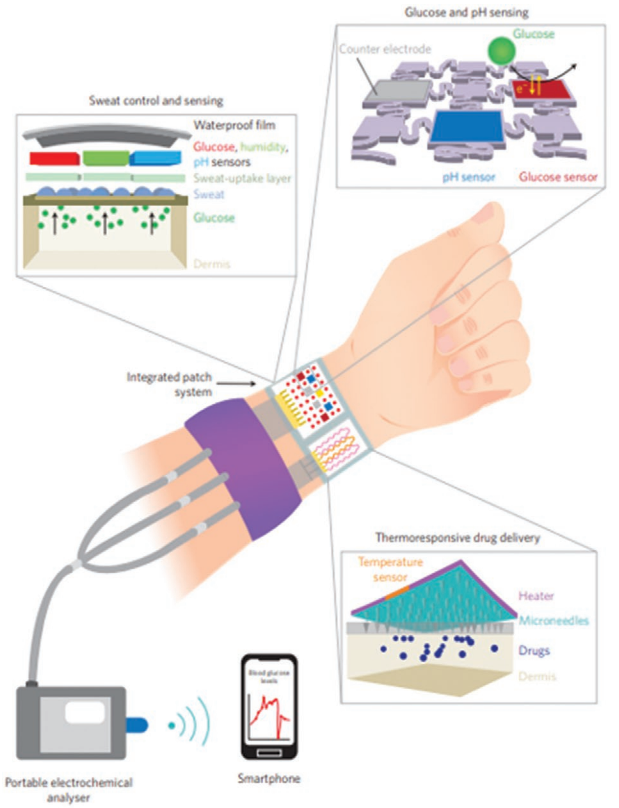

Figure 14. Closed-loop drug delivery systems. An integrated system consists of graphene-based multipixel biosensors for sweat glucose noninvasive monitoring and a thermoresponsive microneedle for diabetes therapy. Reproduced with permission.[116] Copyright 2016, Nature Publishing Group.

tracking combined with VR headset.[119] Based on motion sensors to quantify foot progression angle, it generates real-time visual feedback to instruct the users on gait retraining.

The applications of biosensors for therapeutic system also attribute to their minimized form factors. Recently, Yeo and co-workers constructed an eye vergence tracking system for ocular disorder VR therapies.[120] As shown in Figure 15B, the skin-conformal sensors can be seamlessly applied onto the periocular area, which enable comfortable fitting under a VR headset. The sensing signals were transmitted in a real-time manner, and analyzed based on data classification algorithm. In vivo subjects study demonstrates it as a promising protocol for eye disorder therapies.

Despite the demonstrated benefits and its growing market demand, their clinical implementation is currently limited. The rational sensing network design, extraction of reliable correlations between biosensing signals and body status, as well as the comprehensive big data evaluation are critical to improve the therapy effectiveness.[121] The accuracy and effectiveness for rehabilitation will require careful verification with well-established techniques and laboratory tools.

9. Outlook

The conflicts of large populations and limited clinical resources have triggered huge market demand for wearable and portable healthcare devices. The advances in reliable sensors and rational sensing system design make it possible to perform systematic and statistical studies to reveal the correlations of the targeted biomarkers to our body status. These wearable biosensing systems demonstrate a promise to achieve body computing for personalized healthcare applications.

So far a variety of sensing strategies have been studied and proposed, including physical sensors, chemical sensors, and optoelectronics. The sensitivity and selectivity of wearable biosensing have been largely enhanced with flexible material innovation and the utilization of nanostructured materials. However, to realize accurate body computing in real applications, biosensors with enhanced stability in flexible platforms are expected, especially for its applications in correlation study and closed-loop systems. Several factors including sensor fabrication reproducibility, shelf life, biofouling issue, and mechanical interference still require research efforts on material engineering and device structural optimization. For

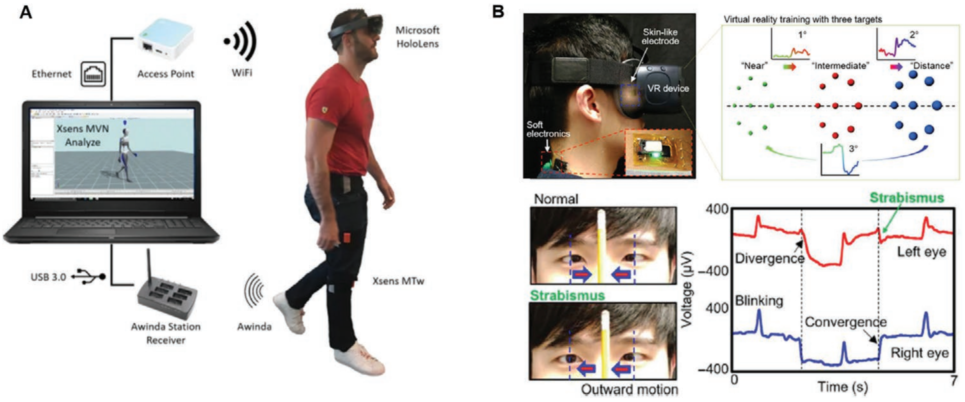

Figure 15. VR-assisted body computing for rehabilitation therapies. A) A wearable biofeedback system using inertial sensors for motion tracking combined with VR headset visual feedback for gait retraining. Reproduced with permission.[119] Copyright 2018, Nature Publishing Group. B) A soft skin-like sensor comfortably fitting under a VR headset for eye disorder therapies. Reproduced with permission.[120] Copyright 2020, AAAS.

instance, biofouling issues can be eliminated with the microfluidic channels to allow fluids refreshing. Besides, it is quite challenging to achieve high sensitivity, desirable selectivity, and decent stability using a single device. For instance, compared with enzymatic sensors, nonenzymatic sensors using electrochemically stable sensing materials (e.g., metal-oxide and polymers), which are much less sensitive to variation of factors such as temperature and pH, are also highly desired for stable sensing, while the challenges mainly exist in its unsatisfying selectivity. One of the promising approaches to address selectivity issues is to utilize multipixels sensors array, utilizing stable active materials in conjunction with reliable sensing signal processing. For instance, by applying AI technology, the specific response patterns from these different sensors to biomarkers can be achieved and the decoding of the compositions/concentrations of the tested fluids can be realized by an automated pattern recognition algorithm. Besides, AI can also provide support to realize the self-calibration capability, so as to ensure the sensing accuracy and achieve calibration-free sensors, which is highly desirable for real applications.

To ensure the functionality of biosensing, energy management of these wearable devices is of significance. Apart from using commercially available power devices, such as batteries, intense research interest has been attracted to the utilization of bioenergy during biosensing. However, the intrinsic unstability of bioenergy might not provide stimulus power output that matches the system requirement. Thus, the incorporation of proper power management strategies, such as hybrid energy harvesting and conversion, and intelligent power control module design is necessary. More research efforts are expected to focus on improving the energy conversion efficiency, power supply durability, as well as parameters matching within these self-powered systems.

The advances in developing robust biosensors, rational sensing system design, energy management module, and reliable sensing data transmission and decoding make it possible to achieve closed-loop wearable system for body computing. These cutting-edge demonstrations of wearable biosensing systems provide attractive routes to a brand-new type of smart sensors with distinguishability among different types of biomarkers for reliable point-of-care applications, which is one of the ultimate goals for biosensors. This will no doubt be a breakthrough and revolution to conventional diagnostic practice, and effectively release the pressure on clinical resources, especially for a society facing the challenge with growing aging populations.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

biosensors, body computing, integrated systems, noninvasive monitoring, wearable electronics

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[1] H. U. Chung, A. Y. Rwei, A. Hourlier-Fargette, S. Xu, K. Lee, E. C. Dunne, Z. Xie, C. Liu, A. Carlini, D. H. Kim, D. Ryu, E. Kulikova, J. Cao, I. C. Odland, K. B. Fields, B. Hopkins, A. Banks, C. Ogle, D. Grande, J. B. Park, J. Kim, M. Irie, H. Jang, J. Lee, Y. Park, J. Kim, H. H. Jo, H. Hahm, R. Avila, Y. Xu, M. Namkoong, J. W. Kwak, E. Suen, M. A. Paulus, R. J. Kim, B. V. Parsons, K. A. Human, S. S. Kim, M. Patel, W. Reuther, H. S. Kim, S. H. Lee, J. D. Leedle, Y. Yun, S. Rigali, T. Son, I. Jung, H. Arafa, V. R. Soundararajan, A. Ollech, A. Shukla, A. Bradley, M. Schau, C. M. Rand, L. E. Marsillio, Z. L. Harris, Y. Huang, A. Hamvas, A. S. Paller, D. E. Weese-Mayer, J. Y. Lee, J. A. Rogers, *Nat. Med.* **2020**, *26*, 418.

[2] J. Heikenfeld, A. Jajack, J. Rogers, P. Gutruf, L. Tian, T. Pan, R. Li, M. Khine, J. Kim, J. Wang, J. Kim, *Lab Chip* **2018**, *18*, 217.

[3] Y. Yu, H. Y. Y. Nyein, W. Gao, A. Javey, *Adv. Mater.* **2020**, *32*, 1902083.

[4] T. Yokota, T. Nakamura, H. Kato, M. Mochizuki, M. Tada, M. Uchida, S. Lee, M. Koizumi, W. Yukita, A. Takimoto, T. Someya, *Nat. Electron.* **2020**, *3*, 113.

[5] J. T. Reeder, Y. Xue, D. Franklin, Y. Deng, J. Choi, O. Prado, R. Kim, C. Liu, J. Hanson, J. Ciraldo, A. J. Bandodkar, S. Krishnan, A. Johnson, E. Patnaude, R. Avila, Y. Huang, J. A. Rogers, *Nat. Commun.* **2019**, *10*, 5513.

[6] M. Bariya, H. Y. Y. Nyein, A. Javey, *Nat. Electron.* **2018**, *1*, 160.

[7] K. Lee, X. Ni, J. Y. Lee, H. Arafa, D. J. Pe, S. Xu, R. Avila, M. Irie, J. H. Lee, R. L. Easterlin, D. H. Kim, H. U. Chung, O. O. Olabisi, S. Getaneh, E. Chung, M. Hill, J. Bell, H. Jang, C. Liu, J. B. Park, J. Kim, S. B. Kim, S. Mehta, M. Pharr, A. Tzavelis, J. T. Reeder, I. Huang, Y. Deng, Z. Xie, C. R. Davies, Y. Huang, J. A. Rogers, *Nat. Biomed. Eng.* **2020**, *4*, 148.

[8] J. Heikenfeld, A. Jajack, B. Feldman, S. W. Granger, S. Gaitonde, G. Begtrup, B. A. Katchman, *Nat. Biotechnol.* **2019**, *37*, 407.

[9] X. Yu, Z. Xie, Y. Yu, J. Lee, A. Vazquez-Guardado, H. Luan, J. Ruban, X. Ning, A. Akhtar, D. Li, B. Ji, Y. Liu, R. Sun, J. Cao, Q. Huo, Y. Zhong, C. Lee, S. Kim, P. Gutruf, C. Zhang, Y. Xue, Q. Guo, A. Chempakasseril, P. Tian, W. Lu, J. Jeong, Y. Yu, J. Cornman, C. Tan, B. Kim, K. Lee, X. Feng, Y. Huang, J. A. Rogers, *Nature* **2019**, *575*, 473.

[10] L.-C. Tai, T. S. Liaw, Y. Lin, H. Y. Y. Nyein, M. Bariya, W. Ji, M. Hettick, C. Zhao, J. Zhao, L. Hou, Z. Yuan, Z. Fan, A. Javey, *Nano Lett.* **2019**, *19*, 6346.

[11] J. Kim, A. S. Campbell, B. E. F. de Ávila, J. Wang, *Nat. Biotechnol.* **2019**, *37*, 389.

[12] R. Ghaffari, J. Choi, M. S. Raj, S. Chen, S. P. Lee, J. T. Reeder, A. J. Aranyosi, A. Leech, W. Li, S. Schon, J. B. Model, J. A. Rogers, *Adv. Funct. Mater.* **2020**, *30*, 1907269.

[13] S. B. Kim, J. Koo, J. Yoon, A. Hourlier-Fargette, B. Lee, S. Chen, S. Jo, J. Choi, Y. S. Oh, G. Lee, S. M. Won, A. J. Aranyosi, S. P. Lee, J. B. Model, P. V. Braun, R. Ghaffari, C. Park, J. A. Rogers, *Lab Chip* **2019**, *20*, 84.

[14] M. Bariya, L. Li, R. Ghattamaneni, C. H. Ahn, H. Y. Y. Nyein, L.-C. Tai, A. Javey, *Sci. Adv.* **2020**, *6*, eabb8308.

[15] J. Francis, I. Stamper, J. Heikenfeld, E. F. Gomez, *Lab Chip* **2018**, *19*, 178.

[16] A. Alizadeh, A. Burns, R. Lenigk, R. Gettings, J. Ashe, A. Porter, M. McCaul, R. Barrett, D. Diamond, P. White, P. Skeath, M. Tomczak, *Lab Chip* **2018**, *18*, 2632.

[17] P. P. Samant, M. R. Prausnitz, *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 4583.

[18] D. Bruen, C. Delaney, L. Florea, D. Diamond, *Sensors* **2017**, *17*, 1866.

[19] K. F. Cutting, *Br. J. Community Nurs.* **2003**, *8*, S4.

[20] C. Zuliani, G. Matzeu, D. Diamond, *Electrochim. Acta* **2014**, *132*, 292.

[21] P. D. V. de Almeida, A. M. T. Grégio, M. A. N. Machado, A. A. S. de Lima, L. R. Azevedo, *J. Contemp. Dent. Pract.* **2008**, *9*, 72.

[22] X. Wang, K. E. Kaczor-Urbanowicz, D. T. W. Wong, *Med. Oncol.* **2017**, *34*, 7.

[23] N. J. Van Haeringen, *Surv. Ophthalmol.* **1981**, *26*, 84.

[24] D. A. Dartt, in *Lacrimal Gland, Tear Film, and Dry Eye Syndromes: Basic Science and Clinical Relevance* (Ed: D. A. Sullivan), Advances in Experimental Medicine and Biology, Springer US, Boston, MA **1994**, pp. 1–9.

[25] B. Buszewski, M. Kęsy, T. Ligor, A. Amann, *Biomed. Chromatogr.* **2007**, *21*, 553.

[26] L. Beker, N. Matsuhisa, I. You, S. R. A. Ruth, S. Niu, A. Foudeh, J. B.-H. Tok, X. Chen, Z. Bao, *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 11314.

[27] Y. Lin, M. Bariya, H. Y. Y. Nyein, L. Kivimäki, S. Uusitalo, E. Jansson, W. Ji, Z. Yuan, T. Happonen, C. Liedert, J. Hiltunen, Z. Fan, A. Javey, *Adv. Funct. Mater.* **2019**, *29*, 1902521.

[28] G.-H. Lee, H. Moon, H. Kim, G. H. Lee, W. Kwon, S. Yoo, D. Myung, S. H. Yun, Z. Bao, S. K. Hahn, *Nat. Rev. Mater.* **2020**, *5*, 149.

[29] D. G. Mackanic, T.-H. Chang, Z. Huang, Y. Cui, Z. Bao, *Chem. Soc. Rev.* **2020**, *49*, 4466.

[30] K. Bashandeh, M. Humood, J. Lee, M. Han, Y. Cui, Y. Shi, Y. Huang, J. A. Rogers, A. A. Polycarpou, *Extreme Mech. Lett.* **2020**, *36*, 100650.

[31] Z. Liu, H. Wang, P. Huang, J. Huang, Y. Zhang, Y. Wang, M. Yu, S. Chen, D. Qi, T. Wang, Y. Jiang, G. Chen, G. Hu, W. Li, J. Yu, Y. Luo, X. J. Loh, B. Liedberg, G. Li, X. Chen, *Adv. Mater.* **2019**, *31*, 1901360.

[32] H. Jin, N. Matsuhisa, S. Lee, M. Abbas, T. Yokota, T. Someya, *Adv. Mater.* **2017**, *29*, 1605848.

[33] A. Tudor, L. Florea, S. Gallagher, J. Burns, D. Diamond, *Sensors* **2016**, *16*, 219.

[34] F. J. Zhao, M. Bonmarin, Z. C. Chen, M. Larson, D. Fay, D. Runnoe, J. Heikenfeld, *Lab Chip* **2019**, *20*, 168.

[35] B. Lu, H. Yuk, S. Lin, N. Jian, K. Qu, J. Xu, X. Zhao, *Nat. Commun.* **2019**, *10*, 1043.

[36] B. C. K. Tee, J. Ouyang, *Adv. Mater.* **2018**, *30*, 1802560.

[37] N. Yi, M. R. Abidian, in *Biosynthetic Polymers for Medical Applications*, Vol. *10* (Eds: L. Poole-Warren, P. Martens, R. Green), Woodhead Publishing, Sawston, UK **2016**, p. 243.

[38] A. Hauke, L. S. S. Kumar, M. Y. Kim, J. Pegan, M. Khine, H. Li, K. W. Plaxco, J. Heikenfeld, *Biosens. Bioelectron.* **2017**, *94*, 438.

[39] H. Zhao, Y. Lee, M. Han, B. K. Sharma, X. Chen, J.-H. Ahn, J. A. Rogers, *Nano Today* **2020**, *30*, 100825.

[40] M. Bariya, Z. Shahpar, H. Park, J. Sun, Y. Jung, W. Gao, H. Y. Y. Nyein, T. S. Liaw, L.-C. Tai, Q. P. Ngo, M. Chao, Y. Zhao, M. Hettick, G. Cho, A. Javey, *ACS Nano* **2018**, *12*, 6978.

[41] Z. Jiang, M. O. G. Nayeem, K. Fukuda, S. Ding, H. Jin, T. Yokota, D. Inoue, D. Hashizume, T. Someya, *Adv. Mater.* **2019**, *31*, 1970265.

[42] A. Miyamoto, S. Lee, N. F. Cooray, S. Lee, M. Mori, N. Matsuhisa, H. Jin, L. Yoda, T. Yokota, A. Itoh, M. Sekino, H. Kawasaki, T. Ebihara, M. Amagai, T. Someya, *Nat. Nanotechnol.* **2017**, *12*, 907.

[43] Z. Xue, H. Song, J. A. Rogers, Y. Zhang, Y. Huang, *Adv. Mater.* **2020**, *32*, 1902254.

[44] J. A. Fan, W. H. Yeo, Y. Su, Y. Hattori, W. Lee, S. Y. Jung, Y. Zhang, Z. Liu, H. Cheng, L. Falgout, M. Bajema, *Nat. Commun.* **2014**, *5*, 3266.

[45] K. Kim, J. Kim, B. G. Hyun, S. Ji, S.o-Y. Kim, S. Kim, B. W. An, J.-U. Park, *Nanoscale* **2015**, *7*, 14577.

[46] W. Fan, Q. He, K. Meng, X. Tan, Z. Zhou, G. Zhang, J. Yang, Z. L. Wang, *Sci. Adv.* **2020**, *6*, eaay2840.

[47] E. Song, J. Li, S. M. Won, W. Bai, J. A. Rogers, *Nat. Mater.* **2020**, *19*, 590.

[48] K. Kwon, S. Y. Heo, I. Yoo, A. Banks, M. Chan, J. Y. Lee, J. B. Park, J. Kim, J. A. Rogers, *Sci. Adv.* **2019**, *5*, eaay2462.

[49] J. Kim, J. R. Sempionatto, S. Imani, M. C. Hartel, A. Barfidokht, G. Tang, A. S. Campbell, P. P. Mercier, J. Wang, *Adv. Sci.* **2018**, *5*, 1800880.

[50] Y. Wang, Y. Qiu, S. K. Ameri, H. Jang, Z. Dai, Y. Huang, N. Lu, *npj Flexible Electron.* **2018**, *2*, 6.

[51] H. Y. Y. Nyein, M. Bariya, L. Kivimäki, S. Uusitalo, T. S. Liaw, E. Jansson, C. H. Ahn, J. A. Hangasky, J. Zhao, Y. Lin, T. Happonen, M. Chao, C. Liedert, Y. Zhao, L.-C. Tai, J. Hiltunen, A. Javey, *Sci. Adv.* **2019**, *5*, eaaw9906.

[52] A. Koh, D. Kang, Y. Xue, S. Lee, R. M. Pielak, J. Kim, T. Hwang, S. Min, A. Banks, P. Bastien, M. C. Manco, L. Wang, K. R. Ammann, K.-I. Jang, P. Won, S. Han, R. Ghaffari, U. Paik, M. J. Slepian, G. Balooch, Y. Huang, J. A. Rogers, *Sci. Transl. Med.* **2016**, *8*, 366ra165.

[53] W. Gao, S. Emaminejad, H. Y. Y. Nyein, S. Challa, K. Chen, A. Peck, H. M. Fahad, H. Ota, H. Shiraki, D. Kiriya, D.-H. Lien, G. A. Brooks, R. W. Davis, A. Javey, *Nature* **2016**, *529*, nature16521.

[54] J. Zhao, Y. Lin, J. Wu, H. Y. Y. Nyein, M. Bariya, L.-C. Tai, M. Chao, W. Ji, G. Zhang, Z. Fan, A. Javey, *ACS Sens.* **2019**, *4*, 1925.

[55] M. Stoppa, A. Chiolerio, *Sensors* **2014**, *14*, 11957.

[56] R. Liu, Q. Shao, S. Wang, C. Ru, D. Balkcom, X. Zhou, *Proc. ACM Interact., Mobile, Wearable Ubiquitous Technol.* **2019**, *3*, 19.

[57] J. Kim, S. Imani, W. R. de Araujo, J. Warchall, G. Valdés-Ramírez, T. R. L. C. Paixão, P. P. Mercier, J. Wang, *Biosens. Bioelectron.* **2015**, *74*, 1061.

[58] P. Tseng, B. Napier, L. Garbarini, D. L. Kaplan, F. G. Omenetto, *Adv. Mater.* **2018**, *30*, 1703257.

[59] S. K. Kim, J. Koo, G. H. Lee, C. Jeon, J. W. Mok, B. H. Mun, K. J. Lee, E. Kamrani, C. K. Joo, S. Shin, J. Y. Sim, *Sci. Adv.* **2020**, *6*, eaba3252.

[60] H. Ota, M. Chao, Y. Gao, E. Wu, L.-C. Tai, K. Chen, Y. Matsuoka, K. Iwai, H. M. Fahad, W. Gao, H. Y. Y. Nyein, L. Lin, A. Javey, *ACS Sens.* **2017**, *2*, 990.

[61] J. R. Sempionatto, T. Nakagawa, A. Pavinatto, S. T. Mensah, S. Imani, P. Mercier, J. Wang, *Lab Chip* **2017**, *17*, 1834.

[62] N. Hegde, M. Bries, E. Sazonov, *Electronics* **2016**, *5*, 48.

[63] D. Popović, L. Popović-Maneski, *EasyChair Preprint* **2019**, 1345.

[64] F. Güder, A. Ainla, J. Redston, B. Mosadegh, A. Glavan, T. J. Martin, G. M. Whitesides, *Angew. Chem., Int. Ed.* **2016**, *55*, 5727.

[65] M. O. G. Nayeem, S. Lee, H. Jin, N. Matsuhisa, H. Jinno, A. Miyamoto, T. Yokota, T. Someya, *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 7063.

[66] S. P. Lee, G. Ha, D. E. Wright, Y. Ma, E. Sen-Gupta, N. R. Haubrich, P. C. Branche, W. Li, G. L. Huppert, M. Johnson, H. B. Mutlu, K. Li, N. Sheth, J. A. Wright, Y. Huang, M. Mansour, J. A. Rogers, R. Ghaffari, *npj Digital Med.* **2018**, *1*, 2.

[67] H. Li, Y. Ma, Z. Liang, Z. Wang, Y. Cao, Y. Xu, H. Zhou, B. Lu, Y. Chen, Z. Han, S. Cai, X. Feng, *Natl. Sci. Rev.* **2020**, *7*, 849.

[68] L. Tian, B. Zimmerman, A. Akhtar, K. J. Yu, M. Moore, J. Wu, R. J. Larsen, J. W. Lee, J. Li, Y. Liu, B. Metzger, S. Qu, X. Guo, K. E. Mathewson, J. A. Fan, J. Cornman, M. Fatina, Z. Xie, Y. Ma, J. Zhang, Y. Zhang, F. Dolcos, M. Fabiani, G. Gratton, T. Bretl,

L. J. Hargrove, P. V. Braun, Y. Huang, J. A. Rogers, *Nat. Biomed. Eng.* **2019**, *3*, 194.
[69] S. Yoon, J. K. Sim, Y.-H. Cho, *Sci. Rep.* **2016**, *6*, 23468.
[70] Y. Gao, H. Ota, E. W. Schaler, K. Chen, A. Zhao, W. Gao, H. M. Fahad, Y. Leng, A. Zheng, F. Xiong, C. Zhang, L.-C. Tai, P. Zhao, R. S. Fearing, A. Javey, *Adv. Mater.* **2017**, *29*, 1701985.
[71] O. Atalay, A. Atalay, J. Gafford, H. Wang, R. Wood, C. Walsh, *Adv. Mater. Technol.* **2017**, *2*, 1700081.
[72] A. J. Bandodkar, P. Gutruf, J. Choi, K. Lee, Y. Sekine, J. T. Reeder, W. J. Jeang, A. J. Aranyosi, S. P. Lee, J. B. Model, R. Ghaffari, C.-J. Su, J. P. Leshock, T. Ray, A. Verrillo, K. Thomas, V. Krishnamurthi, S. Han, J. Kim, S. Krishnan, T. Hang, J. A. Rogers, *Sci. Adv.* **2019**, *5*, eaav3294.
[73] Y. Yang, Y. Song, X. Bo, J. Min, O. S. Pak, L. Zhu, M. Wang, J. Tu, A. Kogan, H. Zhang, T. K. Hsiai, Z. Li, W. Gao, *Nat. Biotechnol.* **2020**, *38*, 217.
[74] Z. Yuan, L. Hou, M. Bariya, H. Y. Y. Nyein, L.-C. Tai, W. Ji, L. Li, A. Javey, *Lab Chip* **2019**, *19*, 3179.
[75] N. Thomas, I. Lähdesmäki, B. A. Parviz, *Sens. Actuators, B* **2012**, *162*, 128.
[76] X. Liu, H. Yuk, S. Lin, G. A. Parada, T. C. Tang, E. Tham, C. de la Fuente-Nunez, T. K. Lu, X. Zhao, *Adv. Mater.* **2018**, *30*, 1704821.
[77] M. S. Mannoor, H. Tao, J. D. Clayton, A. Sengupta, D. L. Kaplan, R. R. Naik, N. Verma, F. G. Omenetto, M. C. McAlpine, *Nat. Commun.* **2012**, *3*, 763.
[78] W. Honda, S. Harada, T. Arie, S. Akita, K. Takei, *Adv. Funct. Mater.* **2014**, *24*, 3298.
[79] W. Jia, X. Wang, S. Imani, A. J. Bandodkar, J. Ramírez, P. P. Mercier, J. Wang, *J. Mater. Chem. A* **2014**, *2*, 18184.
[80] D. Son, J. Lee, S. Qiao, R. Ghaffari, J. Kim, J. E. Lee, C. Song, S. J. Kim, D. J. Lee, S. W. Jun, S. Yang, M. Park, J. Shin, K. Do, M. Lee, K. Kang, C. S. Hwang, N. Lu, T. Hyeon, D.-H. Kim, *Nat. Nanotechnol.* **2014**, *9*, 397.
[81] Z. L. Wang, J. Song, *Science* **2006**, *312*, 242.
[82] A. J. Bandodkar, I. Jeerapan, J. M. You, R. Nuñez-Flores, J. Wang, *Nano Lett.* **2016**, *16*, 721.
[83] I. Jeerapan, J. R. Sempionatto, A. Pavinatto, J.-M. You, J. Wang, *J. Mater. Chem. A* **2016**, *4*, 18342.
[84] W. Jia, G. Valdés-Ramírez, A. J. Bandodkar, J. R. Windmiller, J. Wang, *Angew. Chem., Int. Ed.* **2013**, *52*, 7233.
[85] Y. Yu, J. Nassar, C. Xu, J. Min, Y. Yang, A. Dai, R. Doshi, A. Huang, Y. Song, R. Gehlhar, A. D. Ames, W. Gao, *Sci. Rob.* **2020**, *5*, eaaz7946.
[86] H. Kai, W. Suda, S. Yoshida, M. Nishizawa, *Biosens. Bioelectron.* **2019**, *123*, 108.
[87] J.-H. Bahk, H. Fang, K. Yazawa, A. Shakouri, *J. Mater. Chem. C* **2015**, *3*, 10362.
[88] C. S. Kim, H. M. Yang, J. Lee, G. S. Lee, H. Choi, Y. J. Kim, S. H. Lim, S. H. Cho, B. J. Cho, *ACS Energy Lett.* **2018**, *3*, 501.
[89] Y. Wang, W. Zhu, Y. Deng, B. Fu, P. Zhu, Y. Yu, J. Li, J. Guo, *Nano Energy* **2020**, *73*, 104773.
[90] F.-R. Fan, Z.-Q. Tian, Z. L. Wang, *Nano Energy* **2012**, *1*, 328.
[91] R. Sun, S. C. Carreira, Y. Chen, C. Xiang, L. Xu, B. Zhang, M. Chen, I. Farrow, F. Scarpa, J. Rossiter, *Adv. Mater. Technol.* **2019**, *4*, 1900100.
[92] D. V. Anaya, T. He, C. Lee, M. R. Yuce, *Nano Energy* **2020**, *11*, 104675.
[93] Z. Ren, Q. Zheng, H. Wang, H. Guo, L. Miao, J. Wan, C. Xu, S. Cheng, H. Zhang, *Nano Energy* **2020**, *67*, 104243.
[94] J. Lv, I. Jeerapan, F. Tehrani, L. Yin, C. A. Silva-Lopez, J. H. Jang, R. S. D. Joshuia, Y. Liang, L. Xie, F. Soto, *Energy Environ. Sci.* **2018**, *11*, 3431.
[95] K. Dong, X. Peng, Z. L. Wang, *Adv. Mater.* **2020**, *32*, 1902549.
[96] Y. Lin, J. Chen, M. M. Tavakoli, Y. Gao, Y. Zhu, D. Zhang, M. Kam, Z. He, Z. Fan, *Adv. Mater.* **2019**, *31*, 1804285.
[97] S. Tang, F. Zhang, H. Gong, F. Wei, J. Zhuang, E. Karshalev, B. E.-F. de Ávila, C. Huang, Z. Zhou, Z. Li, L. Yin, H. Dong, R. H. Fang, X. Zhang, L. Zhang, J. Wang, *Sci. Rob.* **2020**, *5*, eaba6137.
[98] Y. Zhang, H. Guo, S. B. Kim, Y. Wu, D. Ostojich, S. H. Park, X. Wang, Z. Weng, R. Li, A. J. Bandodkar, Y. Sekine, J. Choi, S. Xu, S. Quaggin, R. Ghaffari, J. A. Rogers, *Lab Chip* **2019**, *19*, 1545.
[99] Z. Xie, R. Avila, Y. Huang, J. A. Rogers, *Adv. Mater.* **2020**, *32*, 1902767.
[100] X. Tao, T. H. Huang, C. L. Shen, Y. C. Ko, G. T. Jou, V. Koncar, *Adv. Mater. Technol.* **2018**, *3*, 1700309.
[101] H. Y. Y. Nyein, L.-C. Tai, Q. P. Ngo, M. Chao, G. B. Zhang, W. Gao, M. Bariya, J. Bullock, H. Kim, H. M. Fahad, A. Javey, *ACS Sens.* **2018**, *3*, 944.
[102] A. Hauke, P. Simmers, Y. R. Ojha, B. D. Cameron, R. Ballweg, T. Zhang, N. Twine, M. Brothers, E. Gomez, J. Heikenfeld, *Lab Chip* **2018**, *18*, 3750.
[103] L.-C. Tai, C. H. Ahn, H. Y. Y. Nyein, W. Ji, M. Bariya, Y. Lin, L. Li, A. Javey, *ACS Sens.* **2020**, *5*, 1831.
[104] L.-C. Tai, W. Gao, M. Chao, M. Bariya, Q. P. Ngo, Z. Shahpar, H. Y. Y. Nyein, H. Park, J. Sun, Y. Jung, E. Wu, H. M. Fahad, D.-H. Lien, H. Ota, G. Cho, A. Javey, *Adv. Mater.* **2018**, *30*, 1707442.
[105] M. E. Sears, K. J. Kerr, R. I. Bray, *J. Environ. Public Health* **2012**, *2012*, 184745.
[106] C. Delaney, P. McCluskey, S. Coleman, J. Whyte, N. Kent, D. Diamond, *Lab Chip* **2017**, *17*, 2013.
[107] J. T. Reeder, J. Choi, Y. Xue, P. Gutruf, J. Hanson, M. Liu, T. Ray, A. J. Bandodkar, R. Avila, W. Xia, S. Krishnan, S. Xu, K. Barnes, M. Pahnke, R. Ghaffari, Y. Huang, J. A. Rogers, *Sci. Adv.* **2019**, *5*, eaau6356.
[108] R. M. Torrente-Rodríguez, J. Tu, Y. Yang, J. Min, M. Wang, Y. Song, Y. Yu, C. Xu, C. Ye, W. W. IsHak, W. Gao, *Matter* **2020**, *2*, 921.
[109] A. Barmada, S. A. Shippy, *Eye* **2020**, *34*, 1731.
[110] J. R. Sempionatto, L. C. Brazaca, L. García-Carmona, G. Bolat, A. S. Campbell, A. Martin, G. Tang, R. Shah, R. K. Mishra, J. Kim, V. Zucolotto, A. Escarpa, J. Wang, *Biosens. Bioelectron.* **2019**, *137*, 161.
[111] S. L. Swisher, M. C. Lin, A. Liao, E. J. Leeflang, Y. Khan, F. J. Pavinatto, K. Mann, A. Naujokas, D. Young, S. Roy, M. R. Harrison, A. C. Arias, V. Subramanian, M. M. Maharbiz, *Nat. Commun.* **2015**, *6*, 6575.
[112] X. Li, J. Dunn, D. Salins, G. Zhou, W. Zhou, S. M. S.-F. Rose, D. Perelman, E. Colbert, R. Runge, S. Rego, R. Sonecha, S. Datta, T. McLaughlin, M. P. Snyder, *PLoS Biol.* **2017**, *15*, e2001402.
[113] S. M. Schüssler-Fiorenza Rose, K. Contrepois, K. J. Moneghetti, W. Zhou, T. Mishra, S. Mataraso, O. Dagan-Rosenfeld, A. B. Ganz, J. Dunn, D. Hornburg, S. Rego, D. Perelman, S. Ahadi, M. R. Sailani, Y. Zhou, S. R. Leopold, J. Chen, M. Ashland, J. W. Christle, M. Avina, P. Limcaoco, C. Ruiz, M. Tan, A. J. Butte, G. M. Weinstock, G. M. Slavich, E. Sodergren, T. L. McLaughlin, F. Haddad, M. P. Snyder, *Nat. Med.* **2019**, *25*, 792.
[114] H. Teymourian, M. Parrilla, J. R. Sempionatto, N. F. Montiel, A. Barfidokht, R. Van Echelpoel, K. De Wael, J. Wang, *ACS Sens.* **2020**, *5*, 2679.
[115] J. Koo, S. B. Kim, Y. S. Choi, Z. Xie, A. J. Bandodkar, J. Khalifeh, Y. Yan, H. Kim, M. K. Pezhouh, K. Doty, G. Lee, Y.-Y. Chen, S. M. Lee, D. D'Andrea, K. Jung, K. Lee, K. Li, S. Jo, H. Wang, J.-H. Kim, J. Kim, S.-G. Choi, W. J. Jang, Y. S. Oh, I. Park, S. S. Kwak, J.-H. Park, D. Hong, X. Feng, C.-H. Lee,

A. Banks, C. Leal, H. M. Lee, Y. Huang, C. K. Franz, W. Z. Ray, M. MacEwan, S.-K. Kang, J. A. Rogers, *Sci. Adv.* **2020**, *6*, eabb1093.

[116] R. Guy, *Nat. Nanotechnol.* **2016**, *11*, 493.

[117] H. Lee, T. K. Choi, Y. B. Lee, H. R. Cho, R. Ghaffari, L. Wang, H. J. Choi, T. D. Chung, N. Lu, T. Hyeon, S. H. Choi, D.-H. Kim, *Nat. Nanotechnol.* **2016**, *11*, 566.

[118] G. Constantinescu, J.-W. Jeong, X. Li, D. K. Scott, K.-I. Jang, H.-J. Chung, J. A. Rogers, J. Rieger, *Med. Eng. Phys.* **2016**, *38*, 807.

[119] A. Karatsidis, R. E. Richards, J. M. Konrath, J. C. van den Noort, H. M. Schepers, G. Bellusci, J. Harlaar, P. H. Veltink, *J. Neuroeng. Rehabil.* **2018**, *15*, 78.

[120] S. Mishra, Y. S. Kim, J. Intarasirisawat, Y. T. Kwon, Y. Lee, M. Mahmood, H. R. Lim, R. Herbert, K. J. Yu, C. S. Ang, W. H. Yeo, *Sci. Adv.* **2020**, *6*, eaay1729.

[121] M. A. Lopez-Ramirez, F. Soto, C. Wang, R. Rueda, S. Shukla, C. Silva-Lopez, D. Kupor, D. A. McBride, J. K. Pokorski, A. Nourhani, N. F. Steinmetz, N. J. Shah, J. Wang, *Adv. Mater.* **2020**, *32*, 1905740.

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