1

Portable and Wearable Sensing Technologies for Biochemical Detection

*Xin Li, Fenni Zhang, and Qingjun Liu**

Zhejiang University, Biosensor National Special Laboratory, Key Laboratory for Biomedical Engineering of Education Ministry, Department of Biomedical Engineering, No.38, Zheda Road, Hangzhou, 310027, P. R. China

While the first generation of portable or wearable healthcare devices (such as dynamic ECG monitors, oximeters, and sport watches) mainly aims to collect personal physiological information, the advances in biotechnology, miniaturized electronics, and flexible functional materials have fueled the prosperity of portable and wearable biosensor market, which is targeted for disease pre-diagnosis and precise medicine. Owing to their low cost, easy operation, facile readout, and decent detection capability, the arising portable and wearable sensing technologies are highly valued and expected to counter the escalating healthcare demands and challenges. These devices further enable personalized health monitoring and substantially reduce healthcare costs. Coupled with modern data analysis approaches, portable and wearable sensing technologies could open the door for early diagnosis of diseases and precision medicine.

1.1 Biochemical Detection: Increasing Demands and Challenges

Biochemical detections, which measure the biochemical substance (protein, sugar, oxygen, etc.) in body fluid, have been widely used in clinical settings for both disease diagnosis and management. In the past decades, biochemical detections were mainly performed at the laboratory site with bulky and expensive instruments and by specialized professionals for critical disease diagnosis and microbial identification [1]. Nowadays, with the increasing prevalence of the growing population, aging, and chronic diseases continuously rising healthcare costs, the healthcare system is undergoing a vital transformation from a traditional hospital-centered system to an individual-centered system [2, 3]. Therefore, there is an urgent demand for a more efficient method for on-site biochemical detection for applications of critical disease diagnosis and control and for continuous in situ biochemical detection for personal health monitoring and chronic disease management.

* Corresponding author

Portable and Wearable Sensing Systems: Techniques, Fabrication, and Biochemical Detection, First Edition. Edited by Qingjun Liu.

For critical disease diagnosis and control, rapid and accurate biochemical detection for personal precision medicine is still challenging. Many biochemical molecules are present at very low concentrations in complex samples. Infectious diseases are one major type of critical disease, serving as the second leading cause of mortality around the world [4, 5]. The recent outbreaks of life-threatening pandemic diseases (such as the Covid-19 pandemic) have also greatly impacted global healthcare as well as society and economic development [6, 7]. Each infectious disease is caused by specific pathogenic microorganisms, including viruses, bacteria, fungi, and parasites, and rapid and accurate identification of these pathogens is key for controlling the outbreak of threatening infectious diseases. However, the current biochemical detection process of pathogenic microorganisms is complex and requires time-consuming sample processing and multiple detection steps with laboratory equipment, which makes it difficult to meet the actual needs [8]. It is critical to develop rapid on-site detection technology with the availability of easy-to-use, low-cost, and robust diagnostic tests for efficient biochemical detection. The WHO has developed a set of generic guidelines for the development of diagnostic tests appropriate for the developing world that can be summarized under the acronym ASSURED: **af**fordable, **s**ensitive, **s**pecific, **u**ser-friendly, **r**apid and robust, **e**quipment-free, and **d**elivered to those who need it [9].

Except for the rapid and accurate diagnosis and prognosis of acute diseases, in situ biochemical detection is another challenge for the continuous monitoring and management of chronic diseases to achieve personal healthcare and precision medicine. Chronic diseases, such as diabetes and cardiovascular disease, are major health concerns requiring ongoing monitoring and management to prevent them [10]. The human body is a complex biological system, exhibiting a myriad of changing physiological signals that reflect the ongoing physiological processes within the body [11]. The detection and quantification of such real-time biochemical and biophysical signals with body-integrated sensors provide key opportunities for the advancement of personal healthcare. Therefore, there is an increasing demand for developing body-integrated portable and wearable techniques for continuous biochemical monitoring.

1.2 Portable Sensing Technologies: Efficient Biochemical Analysis

As mentioned earlier, biochemical detections play an irreplaceable role in human society. However, conventional biochemical detections are usually limited to the quantitative analysis of various biomarkers and biochemical parameters in biological samples in laboratories under demanding conditions, and the detection process is complex and time consuming [12]. As the economy develops, efficient and portable biochemical detections are in urgent demand for an increasing number of applications [13]. Easily integrated sensing technologies have been designed and developed to meet these needs. In recent years, diverse combinations of technologies have emerged to address the strengths and weaknesses of different detection techniques, greatly improving the detection of biochemical substances, and sensors have been extensively and intensively researched in recent years. As with conventional microbiological detection techniques, the relatively well-developed biochemical techniques combined with biosensors are mostly used for the initial processing of samples. Immunosensors constructed by introducing fast detection speed into biosensors have been widely used for the detection of biochemical substances. Molecular technology, as a new technology, can improve the sensor and is mostly used for the recognition element and signal amplification of the sensor.

With the rapid advances in modern science and technology, this emerging cross-disciplinary field combines the advantages of multiple fields of technology to become an effective biochemical analysis modality with great promise for the rapid and accurate detection and quantification of biochemical substances [14].

As an important analytical technique for biochemical detection, sensing technology is a technique that uses identification elements as biosensing units to convert difficult-to-detect biological signals into detectable signals using appropriate transduction principles. Sensing technology can be used to detect a wide range of analytes in samples of different matrices [15]. The sensors are widely used for their short detection time, fast analysis, and easy integration and have become a popular research area [8].

The increasing demand for rapid and accurate detection of biochemicals is providing opportunities for the development of portable sensing tests [16]. There is a trend to develop miniaturized sensing devices that fully integrate all steps of biochemical testing [3, 17]. Microfluidic systems have been created to improve experimental efficiency and device portability. Compared to other analytical techniques, microfluidics flexibly combines multiple operating units such as sample preparation, reagent manipulation, biological reactions, and detection steps, showing advantages such as system integration, device miniaturization, portability, automation of operating processes, low reagent consumption, elimination of human interference, prevention of contamination, easy integration with other technical equipment, and good compatibility [18, 19]. The aforementioned properties of microfluidic technology have made experiments on a chip a reality from a conceptual point of view. This shift from the traditional central laboratory to experiments on a chip has revolutionized many researchers. Work that previously needed to be done in the laboratory can now be done on a chip. All chambers and valves can be integrated together to perform complex operations with precision. To prevent cross-contamination, different channels for various analyses can be made into closed chambers [20]. Simplify complex analytical protocols and reduce sample volumes, assay times, and reagent costs. Microfluidic technology improves the efficiency and portability of biosensors for outdoor operation, allowing for the simultaneous detection of multiple samples or multiple target microorganisms [21], increasing their utility and flexibility. Li et al. used microfluidic chip fluorescence assays to identify three drug-associated mutational messages from the same sample [22]. The integration of microfluidics with biosensors simultaneously provides the basis for the combination of biosensors and smart devices. They can be made flexible and portable; enable real-time, continuous, and rapid detection; and offer unique advantages such as miniaturization, high sensitivity, and label-free [23]. The introduction of smart devices has greatly improved microbial detection and provided easy data processing and transmission for demonstration purposes. A useful exploration using capillary microfluidic devices in conjunction with smart devices was carried out by Hassan et al. [24]

Among the different biosensing technologies, portable sensing technologies offer great advantages such as simplicity, affordability, portability, and in situ detection capabilities. It plays a key role in several aspects of detection, treatment, economics, health management, and monitoring [2]. Over the past decades, many researchers and scientists have been considering the development of portable sensing technologies with high sensitivity and selectivity for the detection of various biochemical substances [25]. Providing low-cost, user-friendly, and efficient systems with high sensitivity and accuracy is a key step toward rapid detection, accurate quantification, and transferability of data to technicians. Advances in portable sensors are essential to complete the point-of-care testing (POCT) platform [2]. In modern times, the integration of smart nanomaterials in development equipment provides more advanced portable sensors that can produce immediate results and greatly reduce the inspection cycle time. The future of portable sensing technology is likely to be one of high sensitivity and selectivity, miniaturization, versatility, low sample consumption, and high throughput for efficient detection. New advances and improvements are expected to be made through the collaboration and efforts of a diverse community of chemists, physicists, biologists, clinicians, materials scientists, engineering and technology researchers, and others.

1.3 From Portable to Wearable: Toward In Situ Biosensing

1.3.1 Timeline of Major Development in Biosensors

Advances in microelectronics, telecommunications, material science, and bioengineering, together with explosively increasing interest in personalized healthcare monitoring, have propelled the transition of sensory technologies from laboratory-centered to user-centered [26]. Since the prosperity of commercial lateral flow test strips due to their easy use and naked-eye readout in daily practice, portable sensors have witnessed a leap in biochemical detections. Although portable sensors are used to yield qualitative results, their faces have rapidly changed in the last two decades given the progress in microfluidic technologies and augmentable smartphone systems (Figure 1.1). The former factor automates precise sampling of biofluids and multistep sample pretreatment, while smartphones offer abundant hardware and computational resources for designing miniaturized electrochemical and optical sensing systems. These handhold devices facilitate the acquisition of instant information on a wide range of chemicals and biochemicals to indicate individual health status.

Nevertheless, many of the sensing systems still require complex detection procedures and professional skills to operate, thus restraining their use from untrained

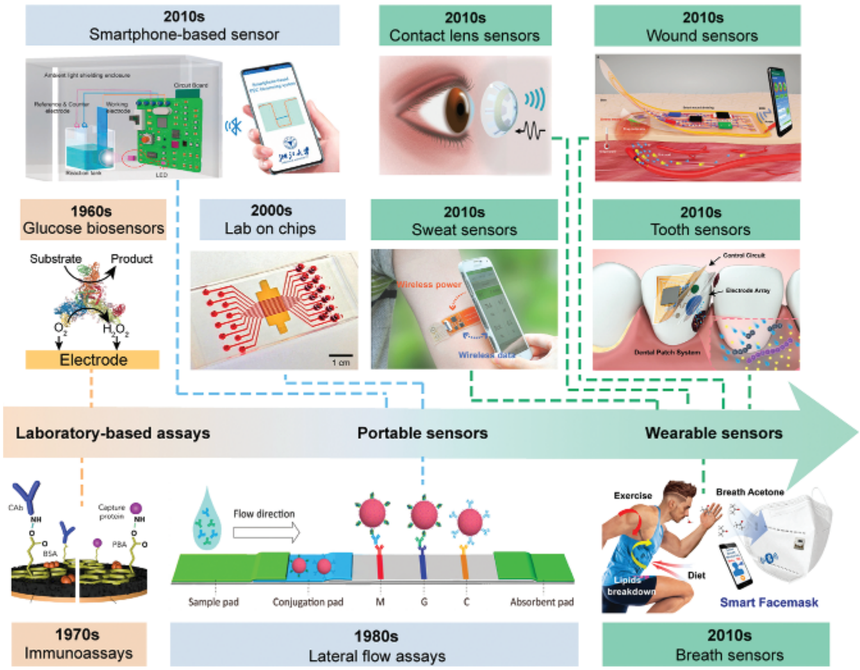

Figure 1.1 Timeline of major development in biosensors from laboratory-based assays to portable sensors and current generation of wearable sensing systems, the advances of which facilitate in situ biosensing for personalized healthcare monitoring. Immunoassays: Source: Reproduced with permission of Ref. [27], © 2020, Elsevier. Smartphone-based sensor: Source: Reproduced with permission of Ref. [28], © 2021, Elsevier. Lateral flow assays. Source: Reproduced with permission of Ref. [29], © 2021, American Chemical Society. Lab on chips: Source: Reproduced with permission of Im et al. [30], © 2014, Springer Nature. Contact lens sensors: Source: From Ref. [31], (2022), Springer Nature, CC BY 4.0. Sweat sensors: Source: Reproduced with permission of Ref. [32], © 2019, John Wiley & Sons. Wound sensors: Source: Reproduced with permission of Ref. [33], © 2021, John Wiley & Sons. Tooth sensors: Source: From Ref. [34], (2022), Springer Nature, CC BY 4.0. Breath sensors: Source: Reproduced with permission of Ref. [35], © 2023, Elsevier.

users. More importantly, although portable detections have established a set of operation protocols, in vitro sampling is still necessary, which introduces issues about sample storage, transfer, and refreshing, thus slitting the temporal and spatial consistency of biochemical detections. Take glucose meter, today's biggest portable sensor market, for example. Each test needs a testing strip and invasive blood collection. Such sensing scheme provides diabetes patients with a more efficient way to guide their diet control and medication; however, it only reflects blood glucose level at certain points. Whereas continuous glucose monitoring is more essential to alarm abnormal blood glucose fluctuation over a longer period of time. Hence, new sensing forms are awaiting to be explored when it comes to scenarios where the needs for fast and continuous updating of sensing results are highly valued.

Ideally, sensing systems with high automaticity, decent accuracy, and capacity to provide real-time biochemical health information would be of particular interest, not only because they can benefit ordinary people in monitoring of daily health status but also because they can reflect more details about disease progression and provide more insights into the fundamental understanding of biochemical metabolism. On this basis, the emergence of wearable sensing systems opened up new avenue toward next generation of medical diagnostic tools. Ever since their inception, wearable sensing technologies have become one of the hottest spots of multidisciplinary science owing to their great potential in real time and in situ biosensing, providing unprecedented knowledge of high-resolution and time-resolved recording of human health profiles [36]. These devices allow for the continuous monitoring of the biochemicals of individuals in a noninvasive or minimally invasive manner, enabling the detection of subtle physiological variations from baseline values over time.

The development of wearable sensing systems did not take off until 2011, when John A. Roger put forward the pathbreaking flexible sensing system incorporating electrophysiological, temperature, and strain sensors, as well as signal conditioning circuits in a tattoo-like device [37]. The epidermal electronics were able to measure electrical activity produced by the heart, brain, and skeletal muscles, demonstrating comparable performances to benchtop laboratory instruments. Apart from physiological monitoring, the focus of wearable sensors has been gradually shifting toward biochemical and multimodal detection of health-related biomarkers in a wide range of bio-samples (Figure 1.1), including biofluids (sweat, tear, saliva, etc.) and breath. A milestone in this category was the multiplexed sweat biosensor system proposed in 2016 for quantitative sweat analysis during exercise [38]. The Berkley team realized real-time glucose, lactate, Na^+, and K^+ detection in sweat, bridging the gap between biosensor design, flexible electronics, signal conditioning, and wireless transmission to fulfill the fully integrated patch-based analytic platform. Not surprisingly, the fusion of flexible circuits and biosensors is compatible with wearable detection of biochemicals around other tissues and organs. Early in 2012, a graphene-based biosensor was integrated onto tooth enamel to detect bacteria [39], while more recently, Shi et al. presented a dental patch for wireless intraoral pH sensing and drug delivery [34]. Another appealing idea would be to functionalize contact lens with flexible antenna and sensitive membrane for tear glucose monitoring [31]. The delicate device provided an efficient tool to analyze the biomarker level in tears in a noninvasive manner, paving the way for personalized medicine and metabolic monitoring. Similarly, proof-of-concepts incorporating wearable sensors with mouthguard [40], urine collector [41], wound dressing [33], and facemask [42] for saliva, urine, wound exudate, and breath analysis have been validated in recent years, respectively. These wearable sensing systems demonstrate the feasibility of utilizing conformal structures to approach the excretion sites of biofluids for facile sample collection and in situ biochemical detection, while compact transducers and miniaturized integrated circuits facilitate continuous and real-time data production without external analytical instruments. Therefore, wearable sensing technologies represent a promising trend in measurement science, contributing to user-centered in situ biosensing for the advancement of physiological monitoring, disease diagnostics, and precise medicine.

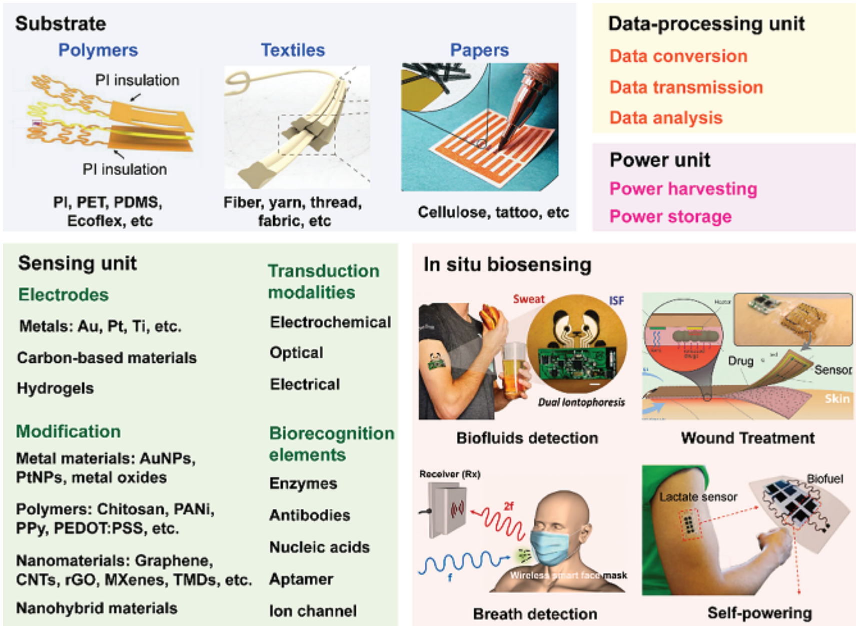

Figure 1.2 Building blocks and applications of wearable sensing systems for biochemical detection. Polymers: Source: Reproduced with permission of Ref. [43], © 2019, John Wiley & Sons. Textiles: Source: Reproduced with permission of Ref. [44], © 2019, John Wiley & Sons. Papers: Source: Reproduced with permission of Ref. [45], © 2012, John Wiley & Sons. Biofluids detection: Source: From Ref. [46], (2018), John Wiley & Sons, CC BY 4.0. Wound treatment: Source: Reproduced with permission of Ref. [47], © 2018, John Wiley & Sons. Breath detection: Source: Reproduced with permission of Ref. [42], © 2022, John Wiley & Sons. Self-powering: Source: Reproduced with permission of Ref. [48], © 2021, John Wiley & Sons.

1.3.2 Building Blocks and Applications of Wearable Sensing Systems

Although the constitutions of wearable sensing systems might vary depending on their structural and functional characteristics, the key building blocks of wearable devices are the substrate, sensing units (including electrodes, modifications, biorecognition elements, and transduction modalities), data-processing units (including circuits for data conversion, transmission, and algorithms for data analysis), and power units (including energy harvesting and storage modules), as shown in Figure 1.2. Rational selection and assembling of these key building blocks are the top priorities in devising applicable wearable devices, as each unit is inner-connected with the others, especially when the overall mechanical strength, stress distribution, and electrical connection layout must be compatible to comfortable wearability.

(1) Substrate

Soft substrate materials serve as the support for sensing, data processing and power units, as well as the interface to human tissues and organs. Appropriate substrates must possess flexibility, biocompatibility, toughness, certain elasticity, and endurance to electronic processing. Generally, polymers, textiles, and papers are the favored choices. Commercialized polymers are especially attractive due to their highly controllable flexibility, functionality, and fabrication ability at industrial scale [45]. This category includes widely investigated polyimide (PI), polyethylene terephthalate (PET), and polydimethylsiloxane (PDMS). Notably, limited lifetime and difficulty in recycling advanced polymers challenge their sustainable use, raising environmental concerns. Textiles and papers, on the other hand, are more environment-friendly substrates for wearable devices. Fibers, yarns, threads, and fabrics made of natural cotton and wool can be easily fabricated into wearables by weaving and knitting. The wearability and biocompatibility of textile substrates exceed their counterparts. However, the intrinsic lack of conductivity and high surface roughness make it more difficult to functionalize textiles into stable electronics. Papers represent another type of promising substrate, mainly owing to their low cost and easy availability. Besides, the progress in conductive functional inks endows versatile patterning of circuits and electronics by screen printing, inkjet printing, extrusion printing, or even direct writing of wearable sensors on papers, thus adding more glamor to the cheap and convenient substrates. Nevertheless, fragile paper sensors have the disadvantage of low mechanical strength and rough surfaces; thus, extra attention should be paid to their stability performance.

(2) Sensing unit

Sensing units are the cores of wearable sensing systems for biochemical detection, which usually consist of layers of laminated electrodes, chemical modifications, and biorecognition elements to realize the transduction of biochemical interfacial information into readable electrical, optical, and electrochemical signals. Specifically, metals with excellent electrical conductivity and metal oxides with optoelectrical characteristics are ideal electrode materials. Gold and platinum with good chemical stability and biocompatibility have been widely investigated as working and counter electrodes in electrochemical systems, while transparent indium tin oxide (ITO) has been the most used optoelectrical interfaces. Carbon-based materials also stand out due to their decent biosafety and conductivity, which facilitate the activity of biorecognition elements and efficient charge transfer. The expanding family of carbon-based nanomaterials such as graphene and graphene oxides, combined with the facile transition of carbon-containing polymers into graphene by laser induction, also strengthens the role of carbon-based electrodes. Despite ultrathin metal electrodes and carbon-based materials demonstrating good transducing performances and fascinating integration compatibility with flexible substrates, the inorganic nature and mismatched mechanical modulus of human tissues restrain their applications, especially when conformal and close tissue-device interfacing is necessary. Recent progress in hydrogel development provides attractive bioelectrode materials. The soft, deformable, and transparent materials, and their hydrophilic properties and porous networks allow for a high water content, which makes them especially biologically friendly. With proper doping of conductive network, hydrogel electrodes would be particularly suitable for biochemical detections involving skin, wound, and tissue implants [49].

Modification of electrodes mainly functions in two aspects: enhancing the immobilization of biorecognition elements and improving signal transducing efficiency. As discussed above, electrodes are usually made of inorganic materials that lack sufficient biocompatibility and surface groups for the immobilization of biorecognition elements. Thus, modifications are introduced to merge the compatibility between bio- and non-bio elements and to improve the loading of biorecognition elements. For instance, gold nanoparticles (AuNPs) are widely used to anchor antibodies and nucleic acids on electrodes via forming stable Au—S bonds [39]. Chitosan serves as a good crosslinker between enzymes and carbon electrodes that are widely used in wearable sweat detection [46]. Besides, to miniaturize the size of wearable devices, the size of electrodes is usually restrained to a millimeter scale or even smaller, which leads to a limited chemically active transduction area. On this basis, modification of nanomaterials could enlarge the surface area via arrangement of low-dimensional nanostructures. Carbon nanotubes (CNTs), graphene, reduced graphene oxides (rGOs), transition metal carbides and nitrides (MXenes), and transition-metal dichalcogenides (TMDs) and their composites have been adopted in various wearable sensing platforms to provide abundant chemical active sites and enhance effective molecular collision for higher sensing signals [50].

The utilization of biorecognition elements distinguishes the second-generation wearable sensors (for biochemical and multimodal detections) from the first generation (for electrophysiology and vital sign monitoring). These components directly link the presence of a biomarker to the sensor output, which must also be compatible with the desired operating mode of the target applications. Generally, biorecognition elements can be both natural and synthetically selected acceptors, including enzymes, antibodies, ion channels, nucleic acids, and aptamers. Enzymes such as glucose oxidase and lactate oxidase are among the earliest biorecognition elements applied in wearable sensors, considering the abundant presence of these small metabolites in biofluids. Besides, enzyme-based sensors produce sustainable output by catalyzing redox events; thus, they can endure a longer term of wearable detection theoretically. However, maintaining enzyme activity is essential for practical use. Antibodies are affinity proteins that bind to target biomarkers, usually proteins, hormones, carbohydrates, pathogens, etc. For instance, wearable platforms integrating cortisol antibodies and cytokine antibodies have been validated in mental pressure evaluation and wound monitoring, respectively [47]. Nevertheless, harsh dissociation steps and auxiliary microfluidic systems are needed to refresh antibody-target bindings, up-to-date wearable antibody sensors are single-used demonstrations. Similar to antibodies, the biorecognition events of nucleic acids and aptamers (fragments of nucleic acids or peptides) are generally irreversible in wearable sensors. It is noticeable that aptamer design can accelerate the selection, enrichment, and generation of binding elements that can rival antibodies in terms of binding affinity and specificity. The utilization of nucleic acids and aptamers is especially competitive in developing wearable diagnostic tools, such as the early screening of cancer-specific gene expression and rapid detection of contagious pathogens. What is more, ion channels have also been actively adopted in wearable sensors, mainly targeting electrolytes such as K^+, Na^+, and H^+. In situ analysis of electrolytes can be responsible for the assessment of athletic performances and alarm the potential dehydration [38].

Signal transduction modalities refer to the schemes to quantify biochemical signals. To provide continuous data stream over a long period, transduction modalities used in wearable sensors must meet with some criteria. (i) The transduction modalities must be compatible to compact wearable devices, that is, they can be realized with flexible materials and electronics, and they are power-affordable in wearable form. (ii) They should be able to provide facile, readable signals to be processed by subsequent data-processing units. (iii) The transduction should be efficient and renewable to yield continuous data. Always remember, with all the elaborate design and complex fabrication process, we hope the wearable sensing systems can provide insights into the dynamic changes in the biochemical level of individuals with high temporal resolution; thus, continuous transduction updating is essential.

On this basis, electrochemical, optical, and electrical methods are preferred in wearable sensors. Electrochemical transduction is featured with simple configuration and direct quantitative electrical signals that are correlated to analyte concentrations. According to the electrical parameters, electrochemical sensors can be divided into potentiometric, amperometric, voltammetric, and impedance sensors. The easily accessible electrical output together with the flexible deployment of three-electrode system and potentiostat facilitates the integration of the electrochemical method in miniaturized wearable devices. Furthermore, advances in multilayered electrodes modification, biocompatible coatings, and microfluidic integration for uniform sampling or biofluid transport have enabled early demonstrations of the continuous measurement of biochemical and biophysical signals in sweat, breath, tears, and saliva. Optical transduction, on the other hand, mainly relies on absorption-based or reflection-based methods for the quantification of biochemical signals. Among wearable optical sensors, colorimetric ones can be fabricated on soft substrates with low cost and large scale, they can be read by naked eyes or smartphone cameras, thus producing qualitative or semi-quantitative results. Notably, the recent incorporation of synthetic biological circuits into flexible substrates enabled the detection of molecular targets in the breath and the environment by colorimetry and bioluminescence [51]. However, non-colorimetric methods usually require sophisticated optical instruments to detect the signals, therefore hampering their wearable integration. Moreover, some wearable sensors adopt direct electrical transduction in the form of resistance, capacitance, or resonance frequency for biochemical analysis. Such transduction modality is mainly used in wearable gas sensors to track concerned breath biochemicals such as alcohols [52] and acetone [35].

(3) Data-processing unit

Signals obtained from wearable sensors need to be processed into interpretable data for understanding individual health and subsequent decision-making.

Thus, increasing endeavors have been devoting to integrate data-processing units into wearable sensing systems to develop intelligent devices. Besides, wide distribution of wearable sensor networks (a series of interconnected sensors worn or implanted in the body) in larger population creates a diverse database to propel data-driven health prediction and disease diagnosis, which is also eager for built-in data-processing units to assist timely decisions.

Specifically, raw signals collected from sensors, such as current or voltage, go into data conversion modules, where the digital signals are transformed into secondary data. Both hardware and software preprocessing, including filtering and smoothing, may be involved in this stage to separate useful information from noises or background signals. For low-dimensional data (single or highly related sensor results), correlation between digital signals and concentration of the analytes is established with transcendental conversion function, while complicated high-dimensional data (multiplexed and non-correlated sensor results) usually requires feature engineering such as clustering and dimensionality reduction [49]. Later on, the converted data and features can be either locally analyzed and displayed (e.g. on a smartwatch) or transmitted into terminals like a smartphone for visualization. When it comes to data transmission, wireless communication is favored. Considering the flexible compliance and limited power, near-field communication (NFC), radio frequency (RF), bluetooth, ultrasound, and infrared light are the selected techniques [53]. The balance among communication technologies, power supply, and flexible integration is a systematic engineering process that is not only about efficiency but also stability and reliability. Once the data stream reaches to smart terminals, further data analysis is initiated. In this stage, machine learning algorithms can play a key role in extracting highly nonlinear patterns from high-dimensional data to establish decision-making model. The model complexity should match the volume and dimensionality of the data to minimize generalization error. Notably, the selection of machine learning is case-dependent. When data exhibit unique individual patterns, such as the detection of epileptic seizures, learning model that has a low complexity (such as support-vector machines and random forests) are typically more successful. Hence, with proper deployment of data-processing unit, the analytical performances of wearable sensing systems can be further improved, which benefits instant and accurate biochemical detection comparable to standard clinical diagnostics.

(4) Power unit

Power supply is one of the key factors that limits the commercialization of wearable devices for biochemical detection. Continuous and stable supply voltage is required in most wearables to power functional electronics such as microcontrollers, operational amplifiers, and analog-to-digital converters for signal conditioning, processing, and data communication. Although the utilization of ultralow-power chips can cut down the expenditure of sensing process into hundreds of microwatts, wireless communication module consumes far more energy. Thus, it is not surprising that earlier implementations managed to include bulky and rigid batteries in wearable sensing systems. Flexible supercapacitors and photocells although provide softer alternatives, but their energy density and working life are questioned in practical use [54].

Wireless energy harvesting and self-powered sensing technologies have been put forward to address the challenge of continuous wearable monitoring. As a matter of fact, wireless energy harvesting was adopted in the earliest epidermal electronics, which utilized antenna to receive energy from nearby electromagnetic field. RF and NFC-based wearable devices are representative examples of this kind, which have been widely used in sweat analysis, brain oxygen detection, contact lens sensors, implantable electronics, etc. Other remote energy harvesting methods, such as infrared light and ultrasound, have also been proposed, whereas their available power is an order of magnitude less than electromagnetic ones. However, ultrasound and infrared light can be attractive solutions in implantable electronics, as they have longer wavelength that can propagate through bio-tissues with less energy loss. Self-powering sensing technology, on the other hand, includes piezoelectric, triboelectric, thermoelectric, hygroelectric, catalytic generators, or a combination thereof. Each approach takes advantage of specific energy sources in the human body or the external environment. These sources can be used to enable self-powered wearables driven by biomechanical (motion or heat), electromagnetic (light or RF), biochemical (metabolites in bodily fluids), or a combination of processes (such as a hybrid system that combines triboelectric generators with biofuel cells) [53]. Notably, the power demand of wearables depends on the complexity of the measurement (for example, single analyte or multianalyte, continuous or single, and quantitative or qualitative), thus the power demand can be evaluated based on the required sensing modalities to select a suitable power supply strategy.

1.4 Summary and Outlook

Overall, wearable sensing systems designed for biochemical detection focus on biofluids analysis, including sweat, tear, saliva, interstitial fluid (ISF), and urine. Sweat has been intensively investigated due to its easy accessibility and abundant metabolites and electrolytes embedded. However, the excretion rate and evaporation of sweat can lead to dramatic fluctuations of the concentration of analytes; thus, shadow has been cast on the reliability of sweat analysis. Besides, most studies relied on exercise to produce sufficient sweat volume for biosensing, which limited sweat analysis to a narrow aspect. To counter the challenges, flexible microfluidic has been adopted to enable automatic and accurate sweat sampling, while iontophoresis delivers sweat-stimulating compounds, enabling active sweat extraction [46]. Compared with sweat, ISF shares a more similar proteomic and metabolomic profiles to blood, which contains a rich source of biomarkers. Particularly, the cytokines and inflammation factors in ISF provide promising target for noninvasive or minimally invasive monitoring of disease immunoreactions. To realize in situ ISF study, wearable sensing systems usually integrate reverse iontophoresis modules or microneedles for ISF extraction [55]. Similarly, the easy accessibility of tear, saliva, and urine provides convenient noninvasive sample source for in situ biosensing. Whereas the obstacles in achieving substantial progress in wearable analysis of these biofluids lie on two aspects: (i) reliable sampling of biofluids without the influence of physiological events, and (ii) correlation between blood and these biofluid analytes needs to be convinced by independent and large-scale clinical validation.

Wearable breath detection has received considerable attention recently, mainly owing to the facile sample collection and abundant metabolites and exogenous biomarkers embedded. Although bench-top instruments such as selective ion flow tube mass spectrometry demonstrate appealingly accurate and on-line performances in laboratory or hospital centralized breath analysis, ordinary individuals have limited access to them. Delightfully, wearable sensors integrated with accessories such as facemasks provide a convenient tool for breath analysis and have been demonstrated in the detection of hydrogen peroxide [56], alcohol [52], carbon dioxide [57], etc. In addition, wearable immunoassays have also manifested decent sensitivity in virus aerosols screening [51], which facilitates noninvasive and efficient disease diagnosis. Nevertheless, extra attention should be paid to improve the accuracy and selectivity of wearable breath detection, which needs notable sensor engineering and pretreatment modules.

A promising trend in devising wearable devices is to integrate sensing units with topical administration for a close-looped diagnosis and medication treatment. In this case, in situ biosensing of inflammation factors, bacterial metabolic markers, and pathogens could provide direct and continuous monitoring for wound infection evaluation [33]. The close deployment of wearable sensors at wound sites offers a unique view to quantitatively track infection progression, which is essential to guide timely topical administration and to avoid antibiotics abuse. Subsequently, the integrated drug delivery module could respond to increased infection parameters or external stimuli such as heat, pressure, or electricity to release drug molecules. The effectiveness of drug treatment could be evaluated in turn by the wearable sensors, thus fulfilling the close loop. However, current integrated wearable sensing-treatment systems only remain in proof-of-concept, where sufficient drug load and reliable decision-making model between sensing and medication are the major challenges.

Addressing power supply in wearable sensing systems has also become the hotspot recently. For continuous and long-term in situ biosensing, stable and wearable power supply solution is essential. Self-powering sensing strategy is independent of external energy input, which utilizes human motions and biomass energy to activate a sensing system. One attractive example is lactate-based biofuel, which is collects energy from metabolic waste in sweat. Lactate is the product of glucose oxidation during anaerobic respiration, whose concentration in sweat can reach to tens of millimoles [53]. Notably, current self-powering systems can only support the function of basic sensing units, whereas complex circuit modules, especially wireless communication units, are far too energy-demanding for them. Thus, rational power management and data interaction need to be further explored to maximize the application of wearable self-powering systems.

In summary, developments of portable and wearable sensing systems propel the fusion of consumer electronics and medical diagnostic tools. With decades of devotion in these fields and significantly improved analytical performances, the boundary between sensor-based detection and clinical assays has been blurring. In the following chapters, we will introduce the fundamental concepts and sensing techniques of both portable and wearable sensing systems and discuss their state-of-the-art applications.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant No. 81971703) and the Zhejiang Provincial Natural Science Foundation of China (No. LZ23C100001).

References

1 Zhang, D., Lu, Y., Jiang, J. et al. (2015). Nanoplasmonic biosensor: coupling electrochemistry to localized surface plasmon resonance spectroscopy on nanocup arrays. *Biosensors & Bioelectronics* 67: 237–242.

2 Zarei, M. (2017). Portable biosensing devices for point-of-care diagnostics: recent developments and applications. *TrAC Trends in Analytical Chemistry* 91: 26–41.

3 Xie, X., Ma, J., Wang, H. et al. (2022). A self-contained and integrated microfluidic nano-detection system for the biosensing and analysis of molecular interactions. *Lab on a Chip* 22: 1702–1713.

4 Sharma, A., Mishra, R.K., Goud, K.Y. et al. (2021). Optical biosensors for diagnostics of infectious viral disease: a recent update. *Diagnostics (Basel)* 11: 2083.

5 Wang, C., Liu, M., Wang, Z. et al. (2021). Point-of-care diagnostics for infectious diseases: from methods to devices. *Nano Today* 37: 101092.

6 Zhang, Q., Bastard, P., Effort, C.H.G. et al. (2022). Human genetic and immunological determinants of critical covid-19 pneumonia. *Nature* 603: 587–598.

7 Cui, F. and Zhou, H.S. (2020). Diagnostic methods and potential portable biosensors for coronavirus disease 2019. *Biosensors & Bioelectronics* 165: 112349.

8 Ma, J., Du, M., Wang, C. et al. (2021). Advances in airborne microorganisms detection using biosensors: a critical review. *Frontiers of Environmental Science & Engineering* 15: 47.

9 Land, K.J., Boeras, D.I., Chen, X.S. et al. (2019). Reassured diagnostics to inform disease control strategies, strengthen health systems and improve patient outcomes. *Nature Microbiology* 4: 46–54.

10 Hamine, S., Gerth-Guyette, E., Faulx, D. et al. (2015). Impact of Mhealth chronic disease management on treatment adherence and patient outcomes: a systematic review. *Journal of Medical Internet Research* 17: e52.

11 Uhlen, M., Fagerberg, L., Hallstrom, B.M. et al. (2015). Proteomics. Tissue-based map of the human proteome. *Science* 347: 1260419.

12 Shrivastava, S., Trung, T.Q., and Lee, N.-E. (2020). Recent progress, challenges, and prospects of fully integrated mobile and wearable point-of-care testing systems for self-testing. *Chemical Society Reviews* 49: 1812–1866.

13 Chu, S., Wang, H., Ling, X. et al. (2020). A portable smartphone platform using a ratiometric fluorescent paper strip for visual quantitative sensing. *ACS Applied Materials & Interfaces* 12: 12962–12971.

14 Zhang, D. and Liu, Q. (2016). Biosensors and bioelectronics on smartphone for portable biochemical detection. *Biosensors & Bioelectronics* 75: 273–284.

15 Chen, Y.T., Lee, Y.C., Lai, Y.H. et al. (2020). Review of integrated optical biosensors for point-of-care applications. *Biosensors (Basel)* 10: 209.

16 Cesewski, E. and Johnson, B.N. (2020). Electrochemical biosensors for pathogen detection. *Biosensors & Bioelectronics* 159: 112214.

17 Hu, B., Li, J., Mou, L. et al. (2017). An automated and portable microfluidic chemiluminescence immunoassay for quantitative detection of biomarkers. *Lab on a Chip* 17: 2225–2234.

18 Nasseri, B., Soleimani, N., Rabiee, N. et al. (2018). Point-of-care microfluidic devices for pathogen detection. *Biosensors & Bioelectronics* 117: 112–128.

19 Wang, L., Qi, W., Liu, Y. et al. (2021). Recent advances on bioaerosol collection and detection in microfluidic chips. *Analytical Chemistry* 93: 9013–9022.

20 Jing, W., Jiang, X., Zhao, W. et al. (2014). Microfluidic platform for direct capture and analysis of airborne mycobacterium tuberculosis. *Analytical Chemistry* 86: 5815–5821.

21 Liu, L., Shan, D., Zhou, X. et al. (2018). Triplex waveguide-based fluorescence biosensor for multichannel environmental contaminants detection. *Biosensors & Bioelectronics* 106: 117–121.

22 Li, R., Zhou, M., Li, J. et al. (2018). Identifying Egfr-expressed cells and detecting Egfr multi-mutations at single-cell level by microfluidic chip. *Nanomicro Letters* 10: 16.

23 Yang, Y. and Gao, W. (2019). Wearable and flexible electronics for continuous molecular monitoring. *Chemical Society Reviews* 48: 1465–1491.

24 Hassan, S.U., Tariq, A., Noreen, Z. et al. (2020). Capillary-driven flow microfluidics combined with smartphone detection: an emerging tool for point-of-care diagnostics. *Diagnostics (Basel)* 10: 509.

25 Sohrabi, H., Hemmati, A., Majidi, M.R. et al. (2021). Recent advances on portable sensing and biosensing assays applied for detection of main chemical and biological pollutant agents in water samples: a critical review. *TrAC Trends in Analytical Chemistry* 143: 116344.

26 Tu, J., Torrente-Rodríguez, R.M., Wang, M., and Gao, W. (2019). The era of digital health: a review of portable and wearable affinity biosensors. *Advanced Functional Materials* 30: 1906713.

27 Torrente-Rodriguez, R.M., Lukas, H., Tu, J. et al. (2020). Sars-Cov-2 rapidplex: a graphene-based multiplexed telemedicine platform for rapid and low-cost covid-19 diagnosis and monitoring. *Matter* 3: 1981–1998.

28 Zhang, Q., Chen, Z., Shi, Z. et al. (2021). Smartphone-based photoelectrochemical biosensing system with graphitic carbon nitride/gold nanoparticles modified electrodes for matrix metalloproteinase-2 detection. *Biosensors & Bioelectronics* 193: 113572.

29 Chen, R., Ren, C., Liu, M. et al. (2021). Early detection of Sars-Cov-2 seroconversion in humans with aggregation-induced near-infrared emission nanoparticle-labeled lateral flow immunoassay. *ACS Nano* 15: 8996–9004.

30 Im, H., Shao, H., Park, Y.I. et al. (2014). Label-free detection and molecular profiling of exosomes with a nano-plasmonic sensor. *Nature Biotechnology* 32 (5): 490–495.

31 Yang, C., Wu, Q., Liu, J. et al. (2022). Intelligent wireless theranostic contact lens for electrical sensing and regulation of intraocular pressure. *Nature Communications* 13: 2556.

32 Xu, G., Cheng, C., Liu, Z. et al. (2019). Battery-free and wireless epidermal electrochemical system with all-printed stretchable electrode array for multiplexed in situ sweat analysis. *Advanced Materials Technologies* 4: 1800658.

33 Xu, G., Lu, Y., Cheng, C. et al. (2021). Battery-free and wireless smart wound dressing for wound infection monitoring and electrically controlled on-demand drug delivery. *Advanced Functional Materials* 31: 2100852.

34 Shi, Z., Lu, Y., Shen, S. et al. (2022). Wearable battery-free theranostic dental patch for wireless intraoral sensing and drug delivery. *npj Flexible Electronics* 6: 49.

35 Li, X., Pan, J., Wu, Y. et al. (2023). Mxene-based wireless facemask enabled wearable breath acetone detection for lipid metabolic monitoring. *Biosensors & Bioelectronics* 222: 114945.

36 Kim, J., Campbell, A.S., de Avila, B.E., and Wang, J. (2019). Wearable biosensors for healthcare monitoring. *Nature Biotechnology* 37: 389–406.

37 Kim, D.-H., Lu, N., Ma, R. et al. (2011). Epidermal electronics. *Science* 333: 838–843.

38 Gao, W., Emaminejad, S., Nyein, H.Y.Y. et al. (2016). Fully integrated wearable sensor arrays for multiplexed in situ perspiration analysis. *Nature* 529: 509–514.

39 Mannoor, M.S., Tao, H., Clayton, J.D. et al. (2012). Graphene-based wireless bacteria detection on tooth enamel. *Nature Communications* 3: 763.

40 Kim, J., Imani, S., de Araujo, W.R. et al. (2015). Wearable salivary uric acid mouthguard biosensor with integrated wireless electronics. *Biosensors & Bioelectronics* 74: 1061–1068.

41 Jia, Y., Liu, G., Xu, G. et al. (2022). Battery-free and wireless tag for in situ sensing of urinary albumin/creatinine ratio (Acr) for the assessment of albuminuria. *Sensors and Actuators B: Chemical* 367: 132050.

42 Ye, Z., Ling, Y., Yang, M. et al. (2022). A breathable, reusable, and zero-power smart face mask for wireless cough and mask-wearing monitoring. *ACS Nano* 16: 5874–5884.

43 Guo, S., Yang, D., Zhang, S. et al. (2019). Development of a cloud-based epidermal $MoSe_2$ device for hazardous gas sensing. *Advanced Functional Materials* 29: 1900138.

44 Ma, L., Wu, R., Patil, A. et al. (2019). Full-textile wireless flexible humidity sensor for human physiological monitoring. *Advanced Functional Materials* 29: 1904549.

45 Mirica, K.A., Weis, J.G., Schnorr, J.M. et al. (2012). Mechanical drawing of gas sensors on paper. *Angewandte Chemie International Edition In English* 51: 10740–10745.

46 Kim, J., Sempionatto, J.R., Imani, S. et al. (2018). Simultaneous monitoring of sweat and interstitial fluid using a single wearable biosensor platform. *Advanced Science (Weinh)* 5: 1800880.

47 Mostafalu, P., Tamayol, A., Rahimi, R. et al. (2018). Smart bandage for monitoring and treatment of chronic wounds. *Small* e1703509.

48 Lv, J., Yin, L., Chen, X. et al. (2021). Wearable biosupercapacitor: harvesting and storing energy from sweat. *Advanced Functional Materials* 31: 2102915.

49 Ates, H.C., Nguyen, P.Q., Gonzalez-Macia, L. et al. (2022). End-to-end design of wearable sensors. *Nature Reviews Materials* 7: 887–907.

50 Li, X., Lu, Y., and Liu, Q. (2021). Electrochemical and optical biosensors based on multifunctional mxene nanoplatforms: progress and prospects. *Talanta* 235: 122726.

51 Nguyen, P.Q., Soenksen, L.R., Donghia, N.M. et al. (2021). Wearable materials with embedded synthetic biology sensors for biomolecule detection. *Nature Biotechnology* 39: 1366–1374.

52 Li, X., An, Z., Lu, Y. et al. (2021). Room temperature vocs sensing with termination-modified Ti3C2TX MXene for wearable exhaled breath monitoring. *Advanced Materials Technologies* 7.

53 Liu, R., Wang, Z.L., Fukuda, K., and Someya, T. (2022). Flexible self-charging power sources. *Nature Reviews Materials* 7: 870–886.

54 Yang, S.Y., Sencadas, V., You, S.S. et al. (2021). Powering implantable and ingestible electronics. *Advanced Functional Materials* 31: 2009289.

55 Tehrani, F., Teymourian, H., Wuerstle, B. et al. (2022). An integrated wearable microneedle array for the continuous monitoring of multiple biomarkers in interstitial fluid. *Nature Biomedical Engineering* 6: 1214–1224.

56 Maier, D., Laubender, E., Basavanna, A. et al. (2019). Toward continuous monitoring of breath biochemistry: a paper-based wearable sensor for real-time hydrogen peroxide measurement in simulated breath. *ACS Sensors* 4: 2945–2951.

57 Escobedo, P., Fernandez-Ramos, M.D., Lopez-Ruiz, N. et al. (2022). Smart facemask for wireless Co(2) Monitoring. *Nature Communications* 13: 72.