Design and Manufacturing of Soft Electronics for *in situ* Biochemical Sensing

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Abstract

Soft (flexible and stretchable) biosensors have great potential in real-time and continuous health monitoring of various physiological factors, mainly due to their better conformability to soft human tissues and organs, which maximizes data fidelity and minimizes biological interference. Most of the early soft sensors focused on sensing physical signals. Recently, it is becoming a trend that novel soft sensors are developed to sense and monitor biochemical signals in situ in real biological environments, thus providing much more meaningful data for studying fundamental biology and diagnosing diverse health conditions. This is essential to decentralize the healthcare resources towards predictive medicine and better disease management. To meet the requirements of mechanical softness and complex biosensing, unconventional materials, and manufacturing process are demanded in developing biosensors. In this review, we summarize the fundamental approaches and the latest and representative design and fabrication to engineer soft electronics (flexible and stretchable) for wearable and implantable biochemical sensing. We will review the rational design and ingenious integration of stretchable materials, structures, and signal transducers in different application scenarios to fabricate high-performance soft biosensors. Focus is also given to how these novel biosensors can be integrated into diverse important physiological environments and scenarios in situ, such as sweat analysis, wound monitoring, and neurochemical sensing. We also rethink and discuss the current limitations, challenges, and prospects of soft biosensors. This review holds significant importance for researchers and engineers, as it assists in comprehending the overarching trends and pivotal issues within the realm of designing and manufacturing soft electronics for biochemical sensing.

Keywords: soft materials processing and fabrication, biochemical sensing, electrode fabrication, transducer integration

1. Introduction

The human body is a soft and dynamic system with complex biomolecular transport and signaling, tissue development, and organ motion across broad time scales and physical dimensions [1-5]. Monitoring fluctuations in these analytes can provide insights into biochemical processes in the human body, which in turn provides feedback on personal health [6]. Traditionally, biological samples such as blood, urine, and feces have been collected and analyzed in healthcare facilities using expensive and bulky testing equipment, as well as complicated processes [7]. Recently, the development of portable and commercially available biochemical biosensors, such as blood glucose meters, has enabled continuous, rapid, and cost-effective detection in the home or through on-body wearable settings [8]. Nonetheless, to extend the applications of wearables and implantable devices for biology and medicine, it is essential to design and develop new biochemical sensors for in situ, continuous monitoring of various disease biomarkers at different body locations (**Figure 1**).

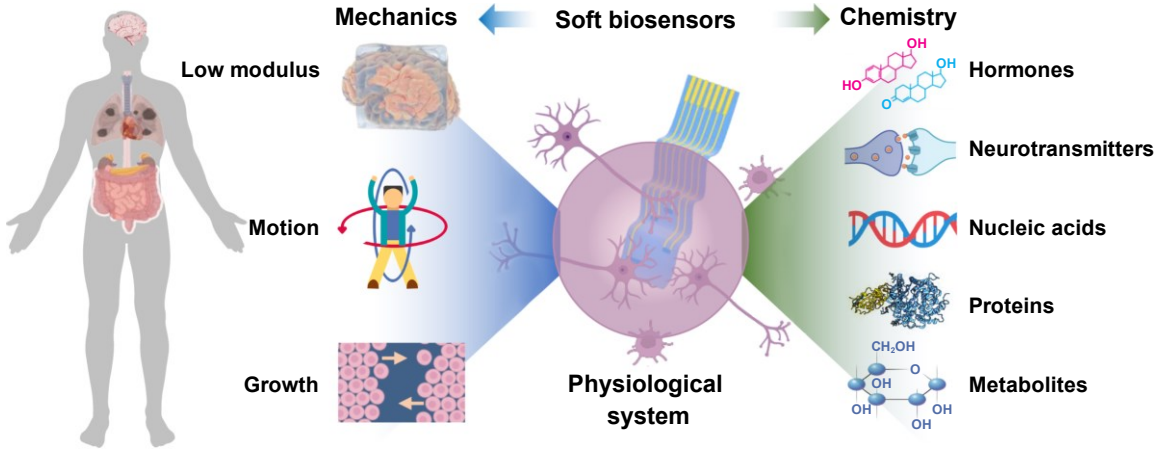

Figure 1. Schematic illustration of soft electronics for in situ biochemical sensing.

Conventional chemical biosensors are usually composed of rigid materials [9]. In contrast, tissues and organs in the human body are soft and curvilinear. The significant difference in mechanical stiffness makes it difficult for conventional chemical biosensors to conform to organs and tissues for precise and continuous in situ sensing (**Table 1**). Deformation due to movement, heart beating, and intestinal peristalsis can further inevitably exacerbate data distortion caused by surface mismatch [10]. In addition, the rigidity of chemical biosensors can cause discomfort and inflammation when worn and implanted because of the accumulation of local pressure and friction. Luckily, the vigorous development of soft bioelectronics provides a feasible way to overcome the mismatch between rigid chemical biosensors and soft tissues [11]. Soft (flexible and stretchable) biosensors can better conform to soft and uneven surfaces of tissues and organs, which maximizes data fidelity and minimizes biological interference [12, 13]. Meanwhile, compared with rigid chemical biosensors, soft chemical biosensors which can be made by solution-processable process are easier to process and prepare at low cost and on a large scale [14]. What's more, soft chemical biosensors can potentially be

biodegradable thus generating less electronic waste [15].

Table 1. Comparison of soft electronics and conventional biosensors.

	Soft electronics	Conventional biosensors
Stiffness	Soft	Rigid
Stretchability	High Deform together with the tissues and maintain functionality; Form an intimate and low-stress bioelectronics interface	Low
Conformability	Partially or fully conformal Low contact impedance; efficient heat, light or mass transfer; Suppressed relative motion; Reduced motion artifacts	Nonconformal
Deployability	3D volumetric integration with tissues and organs	Low
Bioelectronic performance	Low impedance; High signal-to-noise ratio	High impedance; Low signal-to-noise ratio.
Chemical compositions	Organic, more similar to biological tissue	Inorganic, more chemical disparity
Biocompatibility	Improved	Stress accumulation; Inflammatory reactions; Infection and skin irritation; Favorable to bacterial growth and propagation

This review article focuses on the design and fabrication of soft electronics for in situ biochemical sensing (**Figure 1**). It begins by summarizing the systematic approach involving the thoughtful design and effective integration of stretchable structures and materials in various application scenarios to create high-performance soft biosensors. The article also emphasizes how these innovative biosensors can be interfaced with living organs, enabling wearable and implantable sensing applications, including sweat analysis, wound monitoring, and neurotransmitter detection in the brain and gut (**Figure 2**). The review provides a comprehensive and structured framework, covering aspects such as the selection and optimization of stretchable materials and structures, sensor integration techniques, and innovative designs for wearable and implantable devices. It also

offers valuable insights into future research directions and outlines key technological challenges in the field of the design and manufacturing of soft electronics.

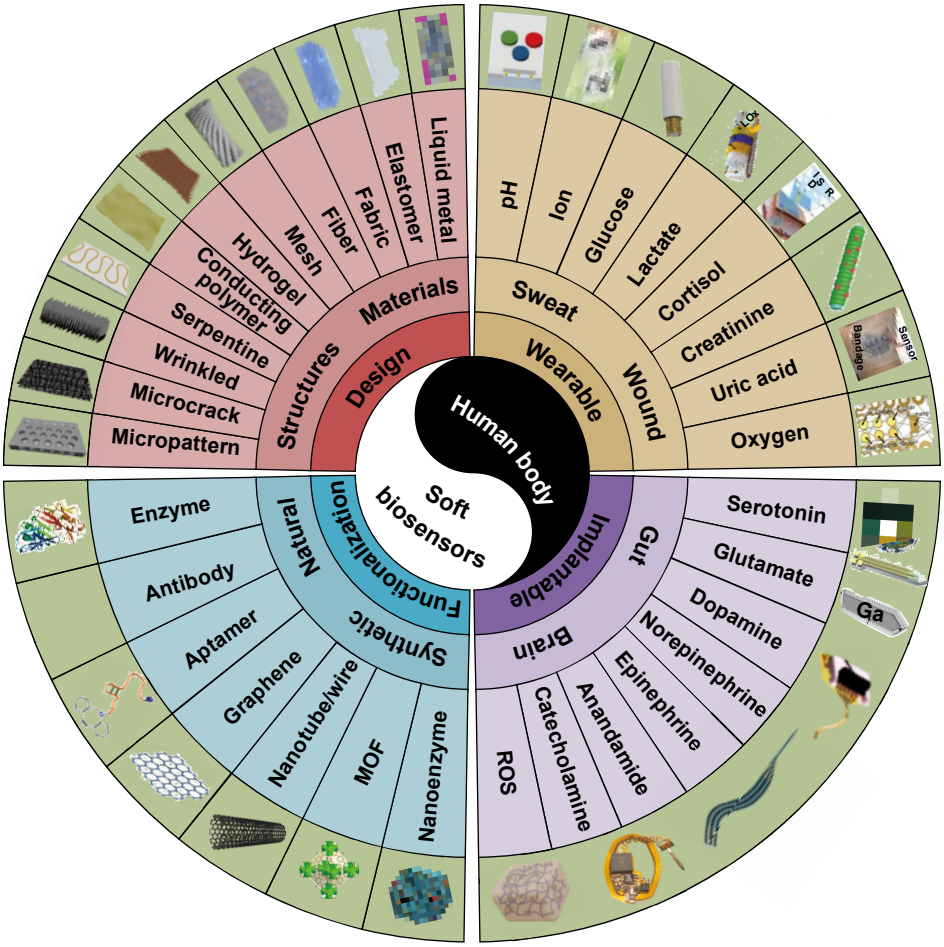

Figure 2. Schematic illustration of the design and functionalization of soft (flexible and stretchable) sensors for wearable and implantable biochemical analysis. Enzyme: Reprinted from [16], Copyright (2022), with permission from Elsevier. Antibody: Reprinted from [17], Copyright (2022), with permission from Elsevier. Aptamer: Reprinted from [18], Copyright (2022), with permission from Elsevier. Graphene: Reprinted from [19], Copyright (2022), with permission from Elsevier. Metal-organic framework (MOF): Reprinted with permission from [20]. Copyright (2020) American Chemical Society. Nanoenzyme: [21] John Wiley & Sons. © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. ROS: [22] John Wiley & Sons. © 2023 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Catecholamine: Reprinted with permission from [23]. Copyright (2023) American Chemical Society.Dopamine: Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nature [24], © 2022. Reprinted with permission from [25] Copyright (2022) American Chemical Society. Glutamate: Reprinted from [26], Copyright (2019), with permission from Elsevier. Serotonin: Reprinted with permission from [27]. Copyright (2021) American Association for the Advancement of Science. [28] John Wiley & Sons. © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Oxygen: Reprinted with permission from [29]. Copyright (2022) American Chemical Society. Uric acid: Reprinted from [30], Copyright (2020), with permission from Elsevier. Creatinine: Reprinted from [31], Copyright (2022), with permission from Elsevier. Cortisol: Reprinted from [32], Copyright (2020), with permission from Elsevier. Lactate: Reprinted from [33], Copyright (2021), with permission from Elsevier. Glucose: Reprinted with permission from [34]. Copyright (2019) American Chemical Society. Ion: [35] John Wiley & Sons. © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. pH: Reprinted with permission from [36]. Copyright (2018) American Chemical Society.

2. Manufacturing of Soft Materials and Structures

Softness and stretchability are crucial for in situ analysis of chemical biosensors [37, 38]. This is mainly because chemical biosensors need to be closely attached to the inherently undevelopable surface of the tissue or organ of the living body during application. At the same time, chemical biosensors are required to be able to produce corresponding deformations and retain original functionality with the stretching or contraction of organs and tissues to achieve precise biosensing [39]. In recent years, stretchable materials and structures have been achieving significant progress [38, 40], which provides a solid foundation and a promising future for the design, preparation, and continuous upgrading and optimization of soft biosensors for biochemical analysis.

2.1 Stretchable structures

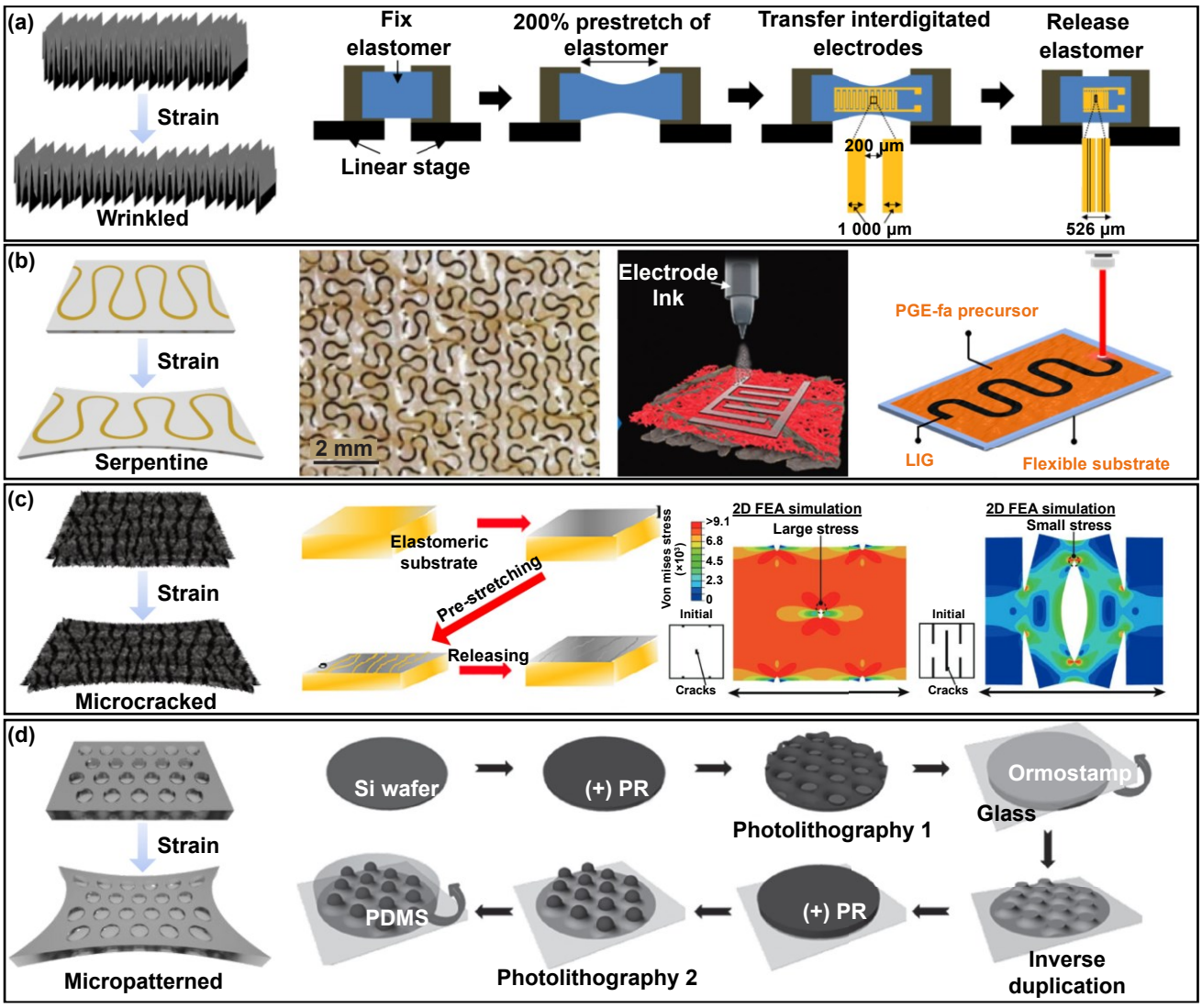

Figure 3. Schematic illustration of stretchable structures. (a) Wrinkled: Reprinted with permission from [41] Copyright (2020) American Association for the Advancement of Science. (b) Serpentine: Reproduced from [42], with permission from Springer Nature. Reproduced from [43] with permission from the Royal Society of Chemistry. Reprinted with permission from [44]. Copyright (2024) American Chemical Society. (c) Microcracked: Reprinted from [45], Copyright (2021), with permission from Elsevier. [46]John Wiley & Sons. © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (d) Micropatterned structures under strain: [47] John Wiley & Sons. © 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Rationale structural design and engineering is an effective way to prepare soft biosensors. For example, as the thickness of the biosensor decreases, the bending stiffness of the biosensor decreases significantly in cubic terms. Based on this proportional relationship, thin-film-like flexible biosensors have been widely developed. To further enhance the stretchability of biosensors, scientists and engineers have designed deterministic geometry structures such as wrinkled (**Figure 3**(a)), serpentine (**Figure 3**(b)), microcracked (**Figure 3**(c)) and micropatterned (**Figure 3**(d)). These structures can effectively reduce the stress of materials though many inorganic materials are used.

Wrinkled structures can relieve the applied strain through the stretching of the wrinkles. Wrinkled structures are typically prepared by releasing a pre-stretched stretchable substrate coated with a rigid film material. In 2007, Rogers and co-workers reported a biaxially stretchable form of wavy silicon nanomembranes that provides an interesting route for the preparation of stretchable, high-performance biosensors [48]. Soleymani's research group fabricated gold wrinkle structures by the thermal shrinking of the polystyrene substance at 140 °C [49]. After transferring the wrinkled gold onto the Ecoflex, the electrical resistance of the fabricated electrodes remained stable at a tensile strain of 30%. Pre-stretching and releasing the elastic material are also suitable for the preparation of wrinkled structures. Benefiting from the simplicity brought by no additional transfer step, the pre-stretching method is more widely used in the preparation of elastomer or fiber electrodes with wrinkled structures. Thakor's research group pre-stretched acrylic elastomer up to 200% by a linear stage and then laminated the gold electrodes on it. After release, the width of the adjacent gold electrodes shrank from 2 200 μm to 526 μm, resulting in the formation of gold-wrinkled structures [41]. Although the introduction of the wrinkled structure will slightly reduce its conformation when it is in direct contact with soft organ or tissue surfaces, it can significantly enhance the performance of the working electrode in liquid sensing after parameter optimization by increasing the contact area and introducing more defects [34].

A wrinkled structure is mainly suitable for the preparation of stretchable electrodes. Meanwhile, the rough outer surface is difficult to conform perfectly to soft biological tissue, hindering the efficient transmission of sensing signals. To address these issues, Rogers's research group designed a variety of serpentine and fractal elements serpentine structures for biosensors, achieving a reversible large deformation response through stress adaptation. For example, they integrated multifunctional sensors containing filamentary serpentine nanoribbons of silicon and gallium arsenide, which offer elastic responses to strain deformations [50]. The serpentine structure resembles a two-dimensional spring in a plane, allowing the sensing device to stretch and twist while improving the conformability of the sensing interface to soft biological tissue. Nowadays, serpentine structures are commonly adopted for the connection of various components of biosensors. With the rapid development of micro-nano manufacturing technology such as photolithography [51], inkjet printing

[52], screen printing [53], and laser scribed technique [44, 45], various serpentine structures have been ameliorated to increase the stretchability of biosensors including the typical bridge-island design [54], filamentary ribbons [55], fractal pattern [42], and triangle lattices [56]. For example, Wang's research group screen-printed a carbon nanotube (CNT)-based electrochemical biosensor by using intrinsically stretchable ink to construct serpentine structures, which can synergistically enhance the stretchability of biosensors [57]. Negligible loss of electrochemical performance and structural changes of the biosensor was observed even when the biosensor was stretched up to 500%.

Micropatterned and microcracked structures are usually built in a planar structure, thus catering to the stretchability requirement of the sensor substrate material. Lee's research group demonstrated that the mogul-patterned structures can enhance the multidirectional stretchability of polydimethylsiloxane (PDMS) substrate, similar to skin tissue [47]. They first adopted double photolithography to fabricate Mogul-patterned glass substrate. They then replicated Mogul-pattern onto PDMS and polyurethane acrylate (PUA) substrate by soft lithography. These two substrates with Mogul-pattern can be used alternately as a mold to prepare Mogul-patterned substrate. For the fabrication of microcrack, Yu's research group electrodeposited nanocrack gold films onto the PDMS substrate [58]. Under 120% uniaxial strain, the stretchable nanocrack gold electrode still possesses good conductivity.

2.2 Stretchable materials

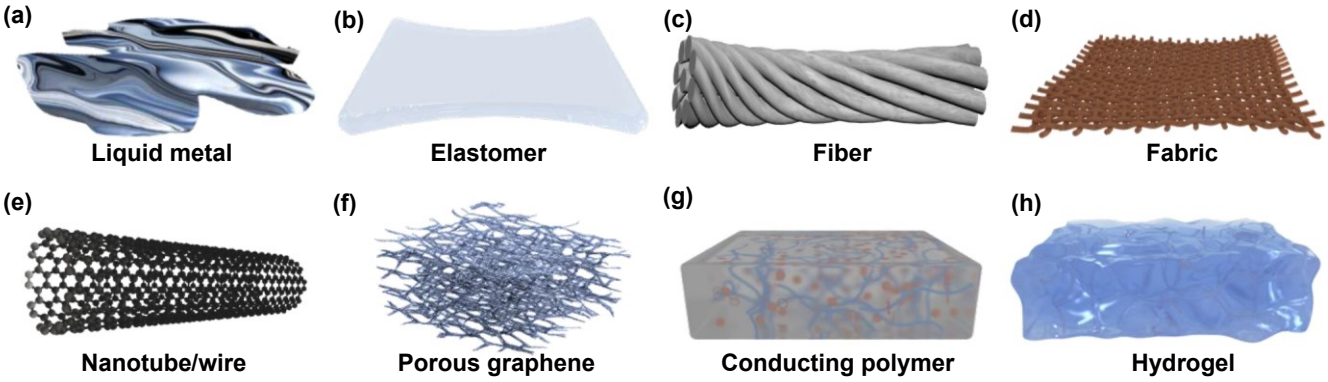

Figure 4. Schematic images of stretchable materials. (a) liquid metal, (b) elastomer, (c) fiber, (d) fabric, (e) nanotube/wire, (f) porous graphene, (g) conducting polymer and (h) hydrogel.

The above structural designs have been proven to be a feasible strategy to effectively reduce the stress for the fabrication of stretchable biosensors. Usually, the metallic materials used to conduct electricity in these stretchable structures are still inherently rigid, and they are encapsulated by stretchable materials or attached to stretchable substrates by deposition or transfer. More importantly, the main purpose of constructing a metal layer with a wrinkled or cracked structure on the surface of the stretchable substrate is to adapt macroscopic deformation. Inherent rigidity may limit their excellent conformation to soft surfaces of biological tissues and organs at the microscopic level. Therefore, flexible and stretchable materials which are stretchable at the

nanoscale or molecular level have been developed to mimic the natural biological tissue for soft biosensors including liquid metal (**Figure 4**(a)) [26, 59-61], elastomer (**Figure 4**(b)) [62, 63], fiber (**Figure 4**(c)) [64], fabric (**Figure 4**(d)) [65], nanotubes/nanowires (**Figure 4**(e)) [66-68], porous graphene (**Figure 4**(f)) [69], conducting polymer (**Figure 4**(g)) [70-73] and hydrogel (**Figure 4**(h)) [74, 75].

Metals occupy an important place in the fields of electronic science and engineering due to their excellent electrical properties. However, they often struggle to withstand large mechanical deformations. Liquid metal gallium and its alloys have excellent electrical conductivity and low melting points. Theoretically, liquid metals can be arbitrarily deformed and maintain high conductivity [76]. Ga and its alloys (GaIn and GaInSn) are very suitable for use as stretchable electrode materials because of the solid-liquid phase transition near body temperature. The most common preparation strategy is to inject liquid metal into a pre-prepared PDMS matrix with microchannels by a pump and then use silicone rubber seals [77]. Differently, Liu's research group used spraying technology to disrupt the liquid metal stream into microdroplets [59]. Liquid metal microdroplets then fell onto the PDMS substrate with a stainless-steel mask and formed a specific shape. The PDMS was finally coated onto the liquid metal layer. This method decreased the cost and cycle of fabrication. In addition, Gozen's research group developed a freeze-printing method to realize the manufacture of 3D nonvertical and freely suspending liquid metal-based structures without the need for a support material [78]. Although liquid metals have excellent conductivity and deformability, the leakage problem that may occur under extreme tensile conditions seriously hinders the improvement of stability and reliability of liquid metal biosensors. Kang's research group combined a long-range assembled network of liquid metal particles and a tough elastomeric matrix [79]. As-prepared liquid metal conductors are highly conductive and mechanically tough. During the stretching process, the liquid metal microparticles deform, while the liquid metal nanoparticles remain stable as interconnectors.

Just as the preparation of stretchable electrodes from liquid metal requires elastomer encapsulation, elastomers with high fracture toughness and low modulus such as PDMS [80], SEBS [24] and Ecoflex [81], are indeed the most widely used materials for the construction of soft biosensors. Besides flexibility and stretchability, elastomers have many other advantages including transparency, chemical inertness, thermal stability and good biocompatibility. As the substrate of biosensors, the surface of elastomer is easy to be functionalized, and it can be firmly combined with the post-modified conductive materials by simple oxygen plasma treatment [82]. Meanwhile, the elastomer is easy to be tailored to diverse shapes and patterns, which meets the needs of large-scale fabrication [83].

In addition to excellent flexibility and stretchability, the requirements for air permeability and skin affinity are also put forward with the continuous development of soft biosensors [84]. Fibers and fabrics can be

modified by metal nanomaterials, carbon nanomaterials, or conductive polymers through impregnation, spinning, or spraying methods, thus achieving flexibility, comfort and conductivity at the same time [64]. For example, Bail's research group used a scalable wet-spinning process to prepare stretchable fibers consisting of polyurethane and silver nanoflowers [85]. The conductivity and the maximum rupture strain achieved 41 245 $S \cdot cm^{-1}$ and 776%, respectively. The resistance of the weft-knitted fabric is almost unchanged under 200% strain. Fibers and fabrics are very suitable as building blocks of biosensors for monitoring physiological signals of strenuous movements such as running and jumping with a large range of strain. In addition, Fang's research group turned the planar rigid device into a fiber-shaped flexible one by replacing the Ti foil with a thin Ti wire. This wearable sensor can monitor the ambient UV power density in real time, which can prevent UV-inducing skin diseases [86].

Carbon-based nanomaterials (carbon nanotubes and graphene flakes) and intrinsic metal nanowires possess high conductivity, inherent softness and tunable mechanical properties [87-90]. Although they are challenging to use individually in the construction of stretchable electrodes, they can be coated onto the surface of a stretchable substrate to provide conductive pathways. Percolation networks between individual nanomaterials can be maintained under stretching. For example, Kim's research group developed a laterally combed nanostructure of a vertically grown CNT network to fabricate a stretchable electrode. At 100% strain, the CNTs can still be well connected, and the change of resistance is very small [91]. Additionally, embedding these conductive nanomaterials with different dimensions into elastomers allows for the creation of elastomeric nanocomposites. These conductive nanomaterials within the elastomer form a 3D conductive percolation network. This percolation network facilitates the free movement of charge carriers through contact junctions and fillers, even under the application of strain and resulting mechanical deformation [92]. Laser-induced graphene nanofiber networks embedded into the SEBS elastomer matrix can achieve 100% strain, which stretchability is far better than graphene monolayer cracking at 5% strain [24]. Nanowires with a high aspect ratio have lower percolation thresholds, resulting in nanocomposites with higher electrical conductivity. The length and diameter of nanowires have a significant impact on the electrical conductivity of elastomeric nanocomposites. In general, as nanowires become longer, electrons can travel greater distances within the nanowires without encountering junctions [93]. As a result, the overall contact resistance in the percolation network is minimized, allowing for high electrical conductivity even under bending conditions. Smaller-diameter nanowires tend to form denser percolation networks, resulting in lower resistance [94].

Intrinsically conductive polymers have a molecular structure containing a conjugated long-chain structure where π electrons on the double bonds can migrate through the molecular chain to form a current, making the polymer structure inherently conductive [95]. Poly(3,4-ethylenedioxythiophene):polystyrene sulfonate

(PEDOT:PSS) with a complex structure based on intimate association of two polyelectrolytes, given the most attention and research, is currently the best conductive polymer for soft biosensors [96]. The commonly accepted structural model of PEDOT:PSS in solution is that small segments of PEDOT in close contact with PSS bundles [73]. Malliaras's research group first realized neuromorphic functions in PEDOT:PSS organic electrochemical transistor [97]. His group also changed the concentration of the additive like 3-glycidoxypropyltrimethoxysilane (GOPS) to co-optimize the electrical, electrochemical and mechanical properties of PEDOT:PSS film [98]. Cui's research group found that hydroxymethylated EDOT (EDOT-MeOH) shows higher solubility in water than EDOT [99]. Doped with PSS, it can significantly decrease the impedance of electrodes. To enhance the conductivity and stretchability of PEDOT:PSS, Zhao's group mixed dimethyl sulfoxide (DMSO) into PEDOT:PSS solutions to redesign the interconnected networks of PEDOT:PSS nanofibrils [100]. The obtained pure PEDOT:PSS hydrogels possess high conductivity and stretchability (> 35%). In addition, Bao's research group designed a topological supramolecular network based on polyethylene glycol (PEG) backbone and sliding cyclodextrins (CDs) functionalized with PEG methacrylate (PEGMA) side chains [101]. This conductive polymer will not crack under 100% strain after microfabrication, showing excellent stretchability. Fang's research group has introduced an innovative design for an ultraflexible, all-organic photodetector. They achieved this by replacing the commonly used indium-doped tin oxide (ITO)/Ag electrodes with symmetrical organic electrodes PH1000/PH1000, resulting in a high self-powered responsivity exceeding 100 $mA \cdot W^{-1}$ in the range of 500 nm ~ 600 nm [102]. This device exhibits remarkable bending resistance, maintaining over 80% of its performance even after undergoing 20 000 folding cycles.

Hydrogels are a class of extremely hydrophilic, three-dimensional network gels formed by the physical or chemical cross-linking of hydrophilic polymers [103-106]. Hydrogels are intrinsically stretchable. Even conventional hydrogels can be stretched to several times their length. Their stretchability can be further improved significantly by optimization, for example by the use of long-chain polymers and cross-linked polymers with reversible physical properties or based on slip-ring mechanisms [107]. Although the higher water content and swelling properties of hydrogels may affect their performance in soft electronic devices, their extraordinary stretchability, biocompatibility and tissue adhesion still make them important in soft biosensors [108]. Zhao's group integrated electronic components and conductors into the hydrogel matrices. The prepared hydrogel electronics and devices are highly stretchable [75]. They also demonstrated that the highly conductive PEDOT:PSS hydrogel (28 $S \cdot cm^{-1}$) can be obtained by the swelling of dry-annealed conducting polymers [109]. In 2021, his research group further invented a graphene nanocomposite hydrogel

with rapid and robust integration with wet tissue surfaces [110]. Meanwhile, the high conductivity (2.6 $S \cdot m^{-1}$) of this composited hydrogel also achieved bioelectronic communications. This work reflects the great potential of hydrogels for the construction of soft biosensors.

2.2 Extreme manufacturing of soft electronics

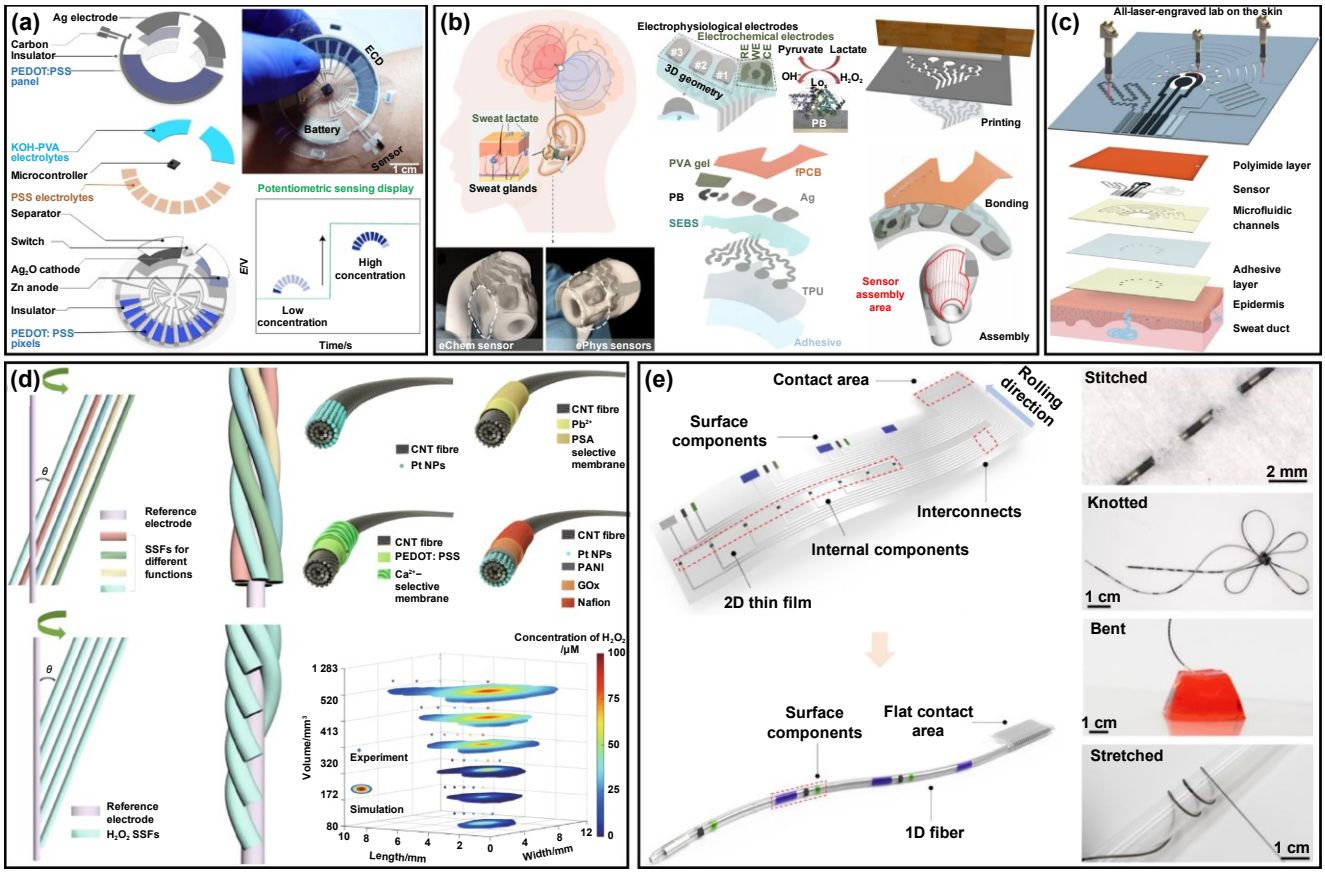

Figure 5. Extreme manufacturing of soft electronics. (a) All-printed skin-interfaced ECD sensing patch. Reproduced from [111], with permission from Springer Nature. (b) In-ear integrated sensors. Reproduced from [112], with permission from Springer Nature. (c) Entirely laser-engraved sensor. Reproduced from [113], with permission from Springer Nature. (d) Functionalized helical fibre bundles of carbon nanotubes as electrochemical sensors. Reproduced from [114], with permission from Springer Nature. (e) Fabrication of Spiral NeuroString showing the transformation of a 2D film with micropatterned components into a 1D fiber and its softness and flexibility. Reprinted from [115], Copyright (2023), with permission from bioRxiv.

Considering the dichotomy between the structure and mechanical properties of soft living tissue and non-living biochemical sensors, several extreme manufacturing techniques have been developed with the aim of achieving a seamless integration and alignment of the structural and mechanical characteristics between electronic systems and biological systems. Wang's research team reported a fully printed epidermal monitoring system, characterized by a compact, flexible, and stretchable design, for non-invasive sweat monitoring (**Figure 5**(a))[111]. This integrated system combines sensors, electrochromic display (ECD), and batteries, enabling users to obtain accurate electrochemical sensing data during regular activities and display them rapidly without the need for external connections. Stable and robust elastomers are utilized as substrates and adhesives, allowing for component fabrication through low-cost, high-throughput layer-by-layer template

printing. The ECD demonstrates color reversibility over more than 10 000 on/off sensing cycles and 1 500 stretch cycles at 20% strain. The battery can power up to 14 000 discrete sensing sessions. This integrated sensing platform is compatible with potentiometric pH and sodium electrolyte sensors, as well as enzyme-based glucose and lactate metabolism biosensors. They further developed an integrated array of electrochemical and electrophysiological sensors within the ear, enabling simultaneous monitoring of lactate concentration, brain state, and skin electrical activity through electroencephalogram, electrooculography, and skin conductance measurements (**Figure 5**(b))[112]. Sensor fabrication utilized rapid, low-cost printing and assembly processes, resulting in a single integrated device with high mechanical elasticity and efficient space utilization. Electrophysiological electrodes were oriented towards the temporal lobe with lower sweat secretion, while electrochemical electrodes were positioned towards areas with higher sweat secretion. The sensors featured a flat-bottomed design with adhesive layers for integration with generic earphone silicone tips. Utilizing a terephthalate polyurethane substrate, stretchable silver ink for serpentine interconnects, lactate sensing electrochemical reference electrodes, SEBS as an insulating layer, and a working electrode based on stretchable Prussian blue ink, conferred outstanding stretchability to the sensor. The three-dimensional structure of the electrophysiological stretchable silver electrodes improved anatomical variations in ear shape and geometric mismatches between the ear canal and earphones. To achieve large-scale manufacturing and multimodal sensing of wearable sweat sensors, Gao's research team reported a fully laser-engraved sensor for continuous detection of temperature, respiration rate, and low concentrations of uric acid and tyrosine. A CO_2 laser cutter was employed to fabricate all the critical components of the sensor: graphene-based chemical sensor, graphene-based physical sensor, and the multi-inlet microfluidic module (**Figure 5**(c))[113].

To enhance the accuracy of readings from implantable biosensors and reduce tissue damage over long-term implantation, several research teams have demonstrated that one-dimensional linear structures hold great promise for constructing implantable sensors due to their lower bending stiffness, which improves mechanical matching between the implanted electronic device and biological tissues. For example, Peng's research team developed a helical fiber bundle composed of twisted functionalized multi-walled carbon nanotubes(**Figure 5**(d))[114]. This helical fiber bundle mimics the layered structure of muscles, exhibits low bending stiffness, and demonstrates ultra-low stress under compression. Twisting single-ply sensing fibers made from differently functionalized carbon nanotubes enables simultaneous monitoring of various disease biomarkers in vivo. When the same type of single-layer sensor fibers is axially distributed within multi-ply sensing fibers, spatial resolution and real-time monitoring of target analytes are achieved. The multifunctionality of the helical fiber bundle as an electrochemical sensor makes it suitable for implantable sensing applications in biomedicine and healthcare. In addition, Bao's research group leveraged the advantages of microfabrication and the ample

surface area available on two-dimensional films to incorporate circuit components, subsequently transforming them into one-dimensional fibers using a spiral technique, which can be used as high-density multimodal soft bioelectronic fibers capable of both sensing and stimulation (**Figure 5**(e)) [115]. The Spiral NeuroString they developed represents a significant enhancement in the density of functional components per unit width of the final device structure compared to conventional planar flat devices. This approach's versatility is evident in the creation of thin electronic fibers with precise control over the devices' angular, radial, and longitudinal positions. Furthermore, in contrast to existing electronic fibers, the Spiral NeuroString not only demonstrates significantly improved flexibility but also offers increased sensing units, density, and functionalities. In another work, Anikeeva's research group introduced multifunctional neural interfaces that blended the scalability and mechanical adaptability of thermally drawn polymer-based fibers with the sophistication of microelectronic chips [116]. Their strategy involves the use of continuous fibers, extending over meters in length, which can seamlessly incorporate elements such as light sources, electrodes, thermal sensors, and microfluidic channels within a compact footprint. Combined with custom-fabricated control modules, these fibers enable wireless delivery of light for optogenetics and the transmission of physiological recording data. These two research efforts have achieved multi-component integration on 1D fiber devices, overcoming the challenge of incompatibility between traditional microfabrication methods like photolithography and the bending, thin, and long structure of optical fibers. The multifunctional microelectronic fibers can establish stable biotic-electronic interfaces in the brains and gastrointestinal tracts of mice. The distinction lies in the former introducing a manufacturing method called spiral transformation, converting 2D thin films containing microfabricated components into 1D soft fibers. This method creates high-density multimodal soft bioelectronic. In vivo sensing methods include, but are not limited to, electrochemical sensing. The latter, essentially, is an extreme manufacturing method based on 1D fibers. They leveraged the scalability of fiber drawing to produce tens of meters of microscale polymer filaments, allowing for the integration of solid-state devices along their surface. This method retains the fiber's excellent mechanical properties while offering unprecedented design flexibility. Embedded microelectronic devices in fiber-based neural probes break their axial redundancy, unlocking new modes of stimulation and sensing supported by solid-state devices. In addition to one-dimensional fibers, three-dimensional mesh electronics probes created via photolithography can be injected using a syringe, simplifying their implantation deep within the brain [117]. Thanks to the inherent self-recovery properties of the grid structure, these mesh electronics probes can naturally expand and conform to the surrounding brain neurons. This technology facilitates high-precision, long-term sensing of brain activity without causing significant inflammation or damage to the brain [66, 118]. Although their previous demonstrations have primarily emphasized the sensing of physical signals, the results presented in their work have substantial potential for various biochemical sensing applications.

2.3 Transducer integration

Transducer integration is essential to achieve highly sensitive and selective biochemical sensing [119]. The top priority is to prepare highly conductive stretchable electrodes with a rational combination of stretchable materials and stretchable structures. The functional modification of the electrode is also crucial to the sensitivity, selectivity, and stability of the working electrodes. In this section, we will introduce the main technologies of transducer integration about electrode fabrication, electrode functionalization and encapsulation.

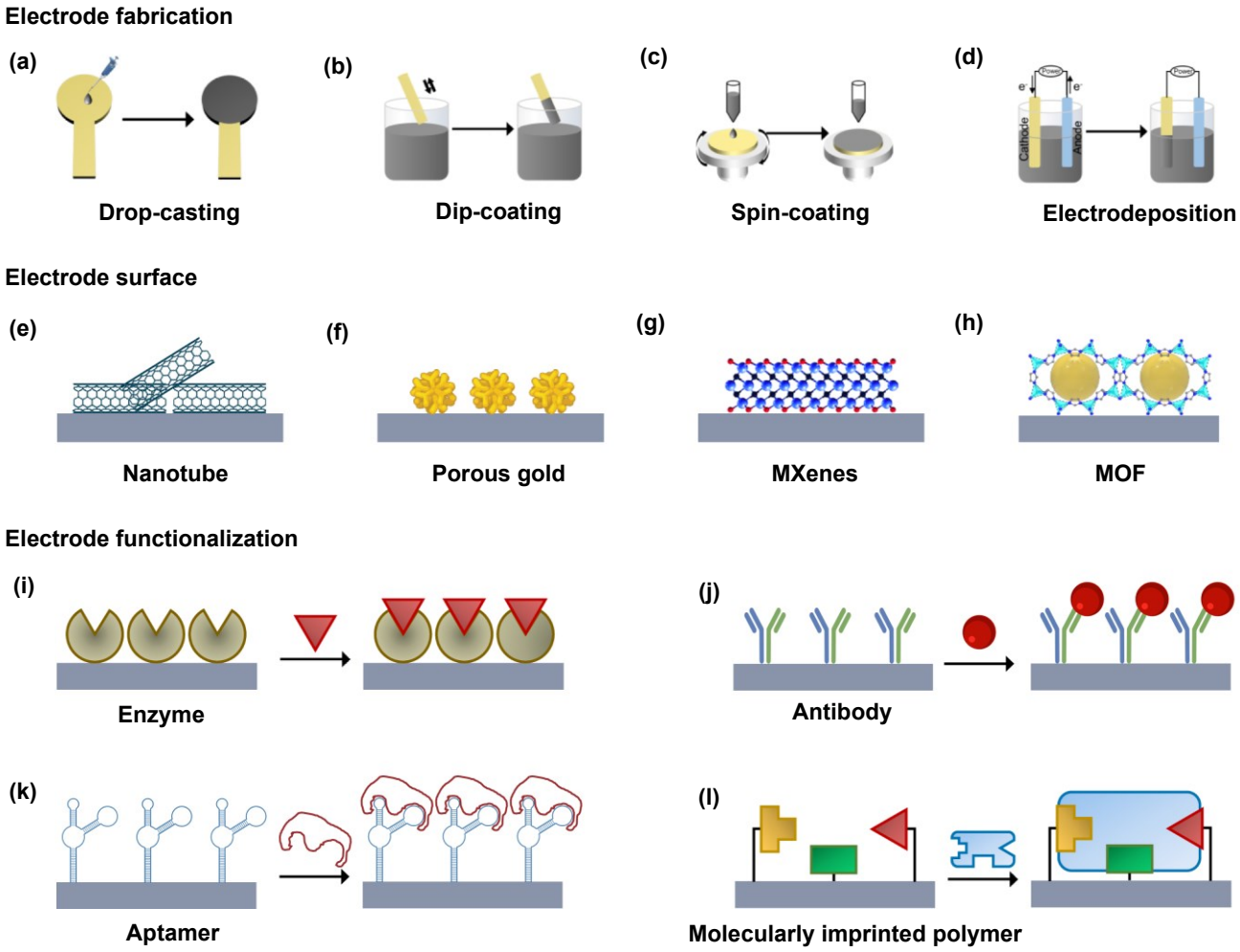

Figure 6. Soft electrode fabrication and functionalization. Schematic illustration of (a) drop-casting, (b) dip-coating, (c) spin-coating, and (d) electrodeposition for electrode fabrication. Materials for enhanced biochemical sensing: (e) nanotube, (f) porous gold, (g) MXenes, and (h) MOF. Schematic illustration of electrode functionalization by (i) enzyme, (j) antibody, (k) aptamer, and (l) molecularly imprinted polymer.

Electrode fabrication of soft biosensors is mainly to integrate high conductivity and stretchability. One preparation route is to post-modify highly conductive components on the surface of the stretchable substrate. The drop coating method is the simplest preparation method. It only needs to drop the nanomaterials or polymer dissolved in the solvent onto the electrode surface. After the solvent evaporates, the solidified film is formed and combined with the electrode surface (**Figure 6**(a)). Cooperation with the filtration method allows

the immobilization of prefabricated nanoparticles onto stretchable substrates, enriching the composition and morphology of electrode surfaces [36]. Dipping and immersion methods (**Figure 6**(b)) gradually adsorb oppositely charged nanomaterials such as Ag nanowires and carbon nanotubes to the electrode surface through electrostatic layer-by-layer self-assembly, which is suitable for stretchable substrates with various shapes [36, 120, 121]. The spin coating method is suitable for the preparation of large areas of film, and the thickness can be precisely controlled by changing the rotation speed (**Figure 6**(c)) [122, 123]. Both electrodeposition and in situ reduction are simple and versatile methods to prepare conductive metal films on the surface of stretchable substrates (**Figure 6**(d)) [34, 58]. Another fabrication route is to directly fabricate composite electrodes with conductive and stretchable components. For example, Cheng's research group used dry spinning technology to directly convert the mixed spinning solution containing AuNWs, styrene−ethylene/butylene−styrene (SEBS) and silicone oil into composite AuNWs/SEBS fibers [34].

Common soft biosensors rely on conductive carbon or gold surfaces due to their high electrochemical stability, conductivity, and the ability to effectively anchor bio-recognition elements. Additionally, functional nanomaterials, such as carbon nanotubes (**Figure 6**(e)), porous gold (**Figure 6**(f)), MXenes (**Figure 6**(g)), and metal-organic framework (MOF) (**Figure 6**(h)), present themselves as potential candidate materials to develop highly sensitive transducer surfaces due to their exceptional electrochemical and optical properties.

Different functionalization methods can be used to prepare working, counter and reference electrodes respectively for constructing electrochemical biosensors. The modification of the working electrode is to realize the specific sensing of the analyte. Natural enzymes can be easily immobilized on the surface of stretchable electrodes by drop-casting (**Figure 6**(i)) [124] or peptide bonds [16]. Wang's group used peroxidase and alkaline phosphatase to develop dual-enzyme-labeling microchip for electrochemical sensing of insulin and cortisol simultaneously [125]. Similarly, Zhang's group dropped glucose oxidase and lactate oxidase onto the Au-coated polyimide working electrode to construct a wearable sweat biosensor [126]. With the rapid development of nanotechnology, the artificially synthesized transition metal oxide nanoparticles, MOFs and nanoenzymes gradually have excellent catalytic activity comparable to that of natural enzymes [127-129]. They are generally more stable than natural enzymes in acidic or alkaline environments [130], and suitable for biosensing in the stomach or infected wounds. Although their selectivity is not as specific as that of natural enzymes, they may apply to the analysis and detection of certain substances. For example, Bao's research group used laser carbonization technology to transform amic acid and ironporphyrin precursors into Fe_3O_4-decorated graphene nanofibers, which can realize the detection of 4 monoamines including dopamine (DA), norepinephrine (NP), serotonin (5-HT) and epinephrine [24]. In addition, antibodies as well as synthetic DNA aptamers can rely on the interaction between sulfhydryl groups and gold (**Figure 6**(j)) [131-135] or strain-promoted azide-alkyne cycloaddition (**Figure 6**(k)) [18] to firmly combine with the electrode surface.

These working electrodes usually have excellent selectivity for the analyte. Molecular imprinting method can format template molecular induced recognition units on polymer substrate (**Figure 6**(l)), mainly including copolymerization with analyte and elution of analyte from polymers [136, 137]. This method does not require additional functionalization modifications and simplifies the preparation steps of the electrode. It also has excellent stability and selectivity. For example, Salleo's research group used cortisol as the molecular template to fabricate molecularly imprinted polymers for cortisol biosensors [138].

Encapsulation allows for a more uniform strain distribution and thus allows the electrodes to retain a higher conductivity under strain. Layer-by-layer stacking is widely used to integrate multiple components (electrode layers, data-transmission layers, and analyte-collection layers) into a single biosensor [139]. Thermoplastic elastomers are the most commonly used encapsulation material, such as PDMS and SEBS [24, 140]. The encapsulation process corresponds to the curing process of the elastomer.

3. Manufacturing and Applications of Wearable Biosensors

3.1 Sweat analysis

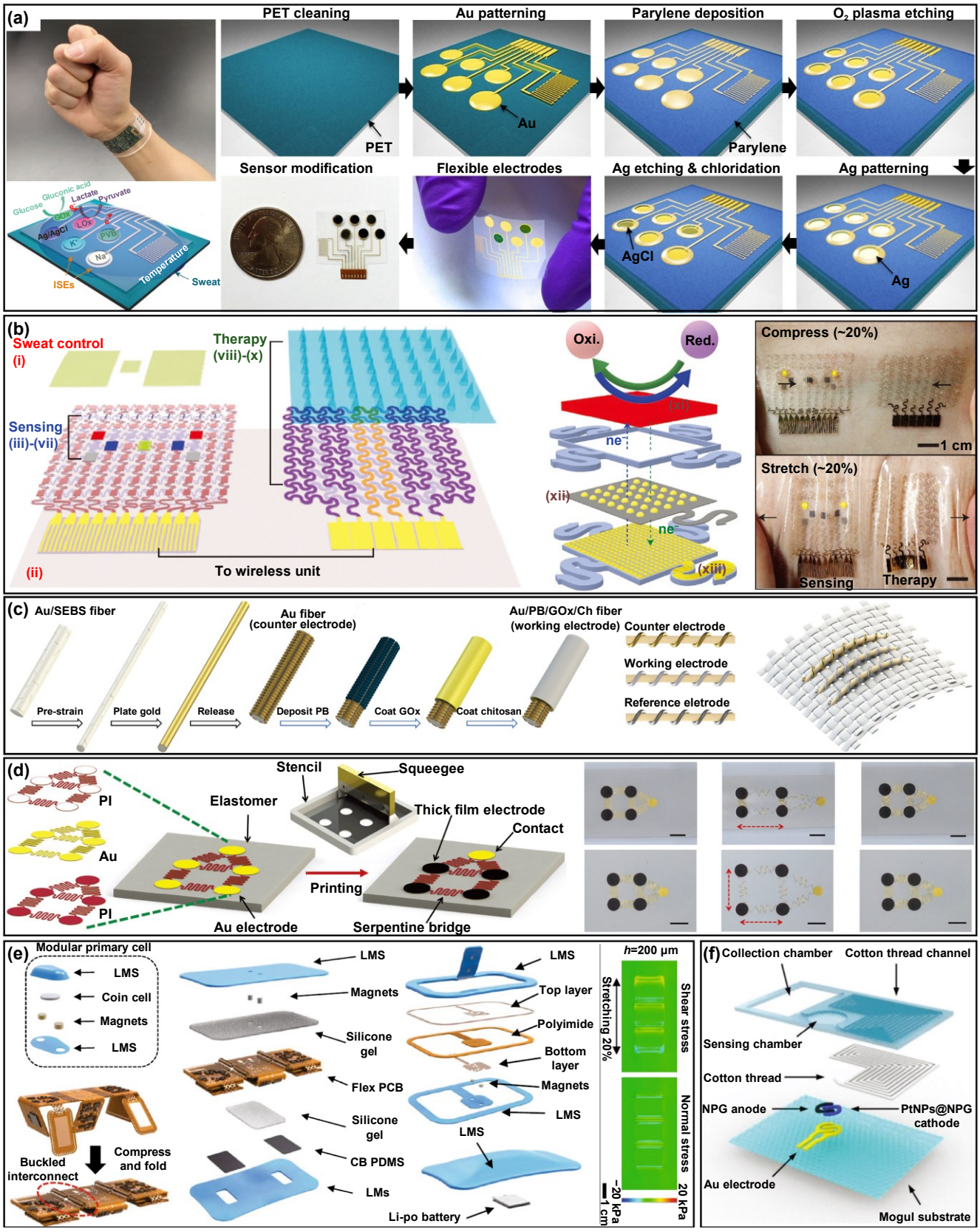

Figure 7. Soft biosensor for wearable sweat analysis. (a) Photograph, schematic and fabrication process of the wearable sensor array for multiplexed perspiration analysis. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nature [13], © 2016. (b) Schematic and photo images of graphene-hybrid stretchable electrochemical biosensors. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nat. Nanotechnol. [141], © 2016. (c) Schematic of the

fabrication process of the stretchable fiber-based sensor by pre-stretching method. Reprinted with permission from [34]. Copyright (2019) American Chemical Society. (d) Schematic of fabrication and stretching of hybrid thick-thin stretchable electrode system. [54] John Wiley & Sons. © 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (e) Schematic illustration of a soft biosensor containing serpentine interconnects, elastomeric enclosure, wireless power-collecting system and powering option. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nat. Med. [142], © 2020. (f) Schematic of the biosensor patch and reaction mechanism of fuel cell. [143] John Wiley & Sons. © 2022 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Wearable sensor technologies are essential to the realization of personalized medicine through continuously monitoring an individual's state of health [13]. Human sweat, an important body fluid that contains metabolites and electrolytes, provides rich information about our health and fitness conditions [144]. Sampling human sweat could enable non-invasive monitoring, avoiding the pain caused by blood tests. [145]. Soft wearable biosensors on the skin can significantly increase comfort and reduce skin irritation. Soft biosensors that conform better to the contours of the skin not only relieve local stress and reduce adverse reactions such as allergies or rashes, but also reduce impedance and thus improve the signal-to-noise ratio [146].

In 2016, Gao *et al*. used photolithography and electron beam evaporation to fabricate a flexible sensor array for multiplexed in situ sweat analysis (**Figure 7**(a)) [13]. This biosensor is fully integrated, which can simultaneously and selectively sense glucose, lactate, Na^+, K^+ and temperature. This design rationally combines skin-fitting plastic sensors and silicon integrated circuit components, overcomes their inherent limitations, and provides a new sensing technology for long-term health detection of human sweat.

Novel carbon materials such as graphene and carbon nanotube (CNT) have many unique advantages such as high conductivity and flexibility, which show great application potential in electronic devices [6, 147-149]. However, the lack of electrochemically active sites makes it difficult to be a building block of electrochemical biosensors alone. To solve this problem, Kim's research group doped gold and graphene to significantly improve the electrochemical performance of bare graphene, catering to the requirements of wearable electrochemical biosensors for monitoring glucose concentration (**Figure 7**(b)) [141]. The combination of a stretchable array and intrinsically soft materials achieved conformal contacts to the deformable skin. Glucose sensing was activated when relative humidity was detected above 80% due to sweating. High glucose concentration triggered the release of Metformin to achieve the feedback drug delivery, offering new opportunities to treat chronic diseases. However, it should be pointed out that the improvement in stretchability of the above device was mainly due to the introduction of the serpentine structure. The sensor module in this system was still not stretchable. To fabricate intrinsically stretchable electrochemical biosensors for sweat analysis, Ha's research group directly filtered Au nanosheets (AuNS) onto the stretchable PDMS substrate in a vacuum, avoiding the additional need for serpentine structures [36]. Layer-by-layer (LbL) deposition was

used to fabricate the working electrode and reference electrode controllably and at low-costly. $CoWO_4$/CNT nanocomposite was deposited as a working electrode to realize non-enzyme glucose sensing. The sensitivity and limit of detection (LOD) of glucose detection were 10.89 $Ma \cdot mM^{-1}$ and 1.3 μM, respectively. Electrodeposition of polyaniline (PANI) was adopted to fabricate another working electrode for pH sensing. The corresponding sensitivity was 71.44 $mV \cdot pH^{-1}$. The extremely stable electrochemical property under deformation was confirmed by 1 000 repetition cycles of stretching/releasing by 30%. Referring to the above design, Lee's research group further improved the sensitivity to glucose (253.4 $\mu A \cdot mM^{-1} \cdot cm^{-2}$) detection by combining the 3D micropatterned PDMS and nanoporous gold while retaining high stretchability [140]. In addition, the collection and handling of sweat are critically important to the accuracy of the measurement. Cotton fabric-based microfluidic channels were introduced for continuous glucose sensing.

MOF, a kind of organic-inorganic hybrid materials formed by self-assembly of organic ligands and metal ions or clusters through coordination bonds, has attracted immense attention due to their high porosity, large specific surface area, rich structure and multi-function [150-152]. Hu's research group designed a highly stretchable fiber-based electrode by wrapping Ni-Co metal-organic frame nanosheets on reduced graphene/polyurethane fibers [153]. Profiting from the high catalytic activity and larger surface area of Ni-Co metal-organic frame nanosheets, this fiber-based electrode possessed a high sensitivity of 425.9 $\mu A \cdot mM^{-1} \cdot cm^{-2}$ and a wide linear range of 10 μM ~ 0.66 mM towards glucose. Liu's research group prestretched the Ecoflex fiber and then modified MCNTs and polyaniline on the fiber surface to fabricate PANI@MWCNT@fiber after relaxing. The immobilization of glucose oxidase (GOx), lactate oxidase (LOx) and creatininase oxidases realized the simultaneous detection of three corresponding chemicals [31].

Cortisol is an important glucocorticoid that regulates carbohydrate metabolism and the immune system in the human body, playing anti-inflammatory, anti-toxin, and hematopoietic effects. Overexpression of cortisol will induce Dementia and Alzheimer's Disease [154]. The cortisol content in sweat is closely related to the cortisol content in the body, and its dynamic monitoring by wearable biosensors can realize the prevention of diseases. Lee's research group fabricated a 3D nanogold working electrode immobilized with cortisol antibody to detect cortisol with pM level [32]. They first deposited Ti/Au onto the Mogul-patterned PDMS substrate. ZnO nanoparticles were spin-coated onto the substrate for growing ZnO nanorods to format 3D nanostructures. 3D nanogold was obtained by the following Au electroplating and ZnO dissolution. Such a stretchable on-a-patch biosensor was competent for daily cortisol measurement, and may assist in warning cortisol-related disease[155, 156]. In addition, Salleo' research group integrated molecularly imprinted polymer membrane of cortisol recognition with water-proof protection layer, sample reservoir and laser-patterned microcapillary channel arrays [138]. As-fabricated biosensors can accurately transport the sample in sweat to the sensor

interface, further realizing both ex situ and on-body cortisol sensing.

Pre-stretch has been demonstrated to be a simple way to prepare stretchable electrochemical biosensors, making full use of the inherent stretchability of substrate materials [41]. For example, Liu's research group coated Cu-CNT on a pre-stretched rubber fiber to fabricate stretchable fiber with core@sheath and hierarchically buckled structures [157]. The resistance was low with a value of 0.4 $\Omega \cdot cm^{-1}$ at 500% strain, only increasing 27% from 0% to 500% strain. The as-prepared Cu-CNT fiber electrode displayed excellent selectivity and linear detection of glucose between 0.05 mM ~ 5 mM within a 60% strain range. Similarly, Cheng's research group adopted the pre-strain method to construct a stretchable three-electrode biosensor for wearable glucose detection (**Figure 7**(c)) [34]. They pre-stretched Au nanowires (AuNWs)/styrene−ethylene/butylene−styrene (SEBS) fibers to 300%, plated AuFilm and followed by release to fabricate Au fibers as a counter electrode. The counter electrode could be subsequently modified with Ag/AgCl or GOx to serve as a reference electrode or working electrode, respectively. Further winding these electrode fibers around elastic fiber cores with 80° winding angles achieved stable electrochemical performance from 0 to 200% strain with a sensitivity of 11.7 $Ma \cdot mM^{-1} \cdot cm^{-2}$ ranging from 0 to 500 μM glucose concentration. Notably, such an AuFilm-modified AuNWs/SEBS can be extended to the detection of other metabolites. For example, a stretchable lactate biosensor could be simply fabricated by substituting LOx for GOx [33]. The sensitivity with a value of 14.6 $\mu A \cdot mM^{-1} \cdot cm^{-2}$ in artificial sweat could be retained even under strain up to 100%. In addition, Wang's research group developed a combination of thick and thin film fabrication techniques to manufacture highly stretchable "island-bridge" devices (**Figure 7**(d)) [54]. Rigid materials can be integrated into the elastic substrate to construct a flexible and stretchable hybrid system, which can withstand 75% strain in either the uniaxial or biaxial direction. Printing diverse enzymes or carbons realized sensitive electrochemical sensing of glucose, lactate, nucleic acids and neurotransmitter.

The above summary mainly focuses on the preparation of stretchable electrodes of biosensors. These stretchable electrodes usually need to be connected to an external electrochemical workstation and battery to achieve data collection and energy acquisition, which significantly reduces the flexibility and portability in actual sweat sensing. It is highly desirable to develop integrated sensor patches for sweat analysis [158-161]. Liu's research group developed a battery-free and wireless stretchable electrochemical biosensor for the detection of glucose, hydrogen, sodium, and potassium in sweat [35]. Stretchable electrode arrays were printed with conductive silver nanowires and PDMS that displayed stable sensing characteristics up to 50% strain. Wireless energy collection and data transmission with smartphones were achieved through the use of integrated flexible circuit boards with near-field communication modules. Roger's research group fabricated a soft skin-interfaced biosensor for physiological monitoring in neonatal and pediatric intensive-care units

(**Figure 7**(e)) [142]. They used pairs of matching sets of embedded magnets to couple the modular battery unit to the soft biosensors. This combination allows medical staff to individually sterilize the sensing components and quickly replace the batteries. Modular coin cells can support operation for 2 h ~ 8 h. The lithium-polymer battery (45 mAh) can increase the operation time to 30 h. This biosensor can also be combined with wireless transmission technology, providing an indefinite lifetime.

In addition to wireless power transfer, glucose in sweat can also be used as an energy source for stretchable biosensors. For example, in **Figure 7**(f), Lee's research group used nanoporous gold (NPG) as an anode and NPG coated with Pt nanoparticles as a cathode to fabricate a stretchable fuel cell-based glucose biosensor [143]. The sensitivity and LOD of this stretchable biosensor for glucose are 62.33 $Mv \cdot M^{-1}$ and 9 μM, respectively. Both the maximum power density and open circuit voltage attenuated less than 5% under 30% elongation strain. Another example is a textile matrix self-powered glucose biosensor designed by Hui's research group [124]. Reduced graphene oxides (RGO) and multiwall carbon nanotubes (MCNTs) were decorated onto the cellulose fiber-based textile matrix to significantly enhance the conductivity of the matrix. GOx and laccase were respectively immobilized onto RGO/MCNTs-coated textile matrix to construct the anode and cathode of the self-powered system. In addition, Liu's research group twinned the varnished wire with PANI@MWCNT@fiber to fabricate a stretchable self-powered biosensor based on a triboelectric nanogenerator [31]. When the deformation of the wearer's joint movement occurred, the sensor generated friction to provide sufficient power for the biosensor.

3.2 Wound monitoring

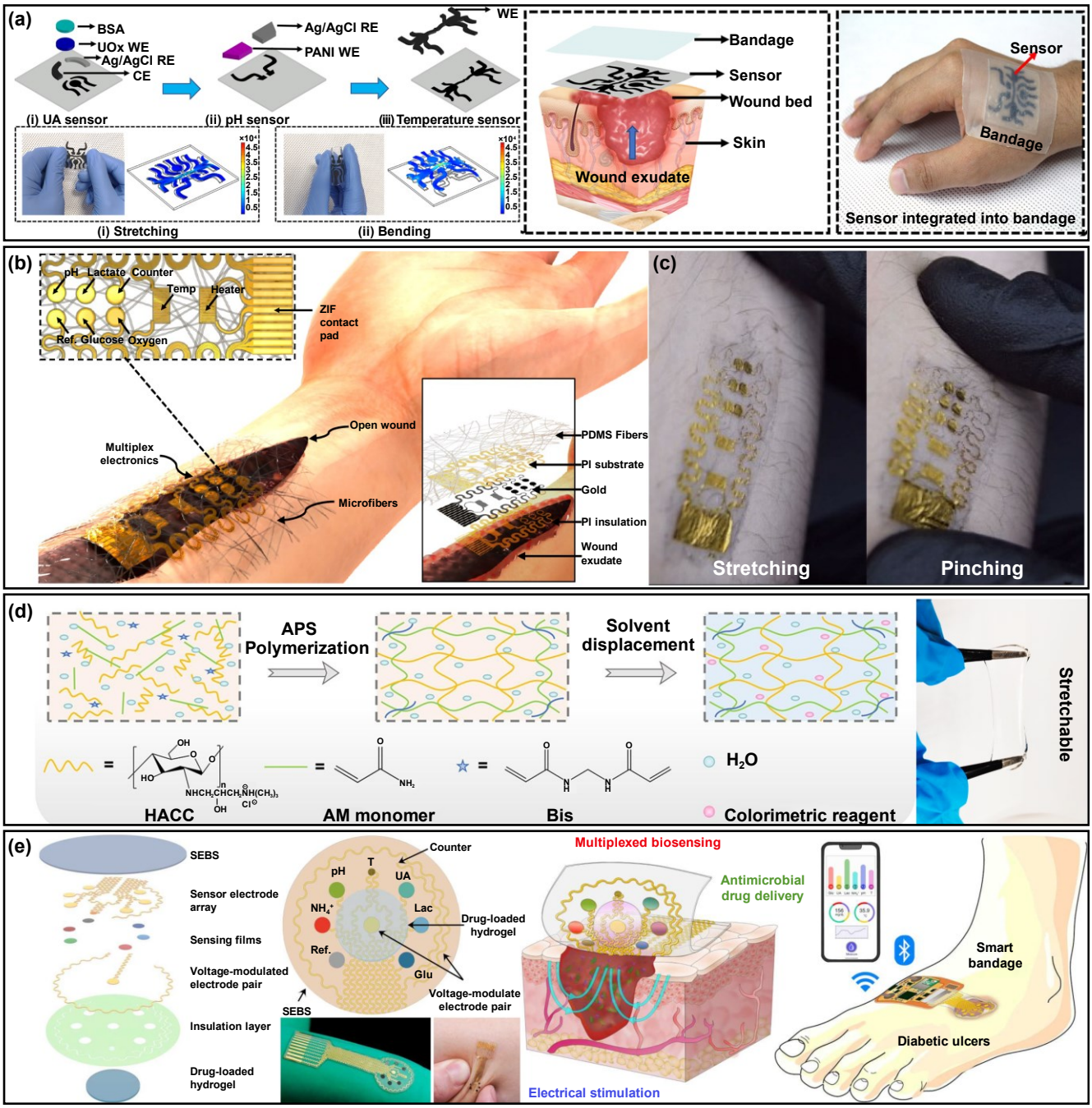

Figure 8. Soft biosensor for wearable wound monitoring. (a) Schematic of the fabrication of the stretchable and flexible smart bandage biosensor for wound care management. Reprinted from [30], Copyright (2020), with permission from Elsevier. (b) Schematic of electronic-extracellular matrix (e-ECM) wound care biosensor. (c) Photo images of e-ECM biosensor under stretching and pitching. Reprinted with permission from [29]. Copyright (2022) American Chemical Society. (d) Schematic preparation of multifunctional hydrogel composed of polyacrylamide and chitosan quaternary ammonium salt. Reprinted from [162], Copyright (2022), with permission from Elsevier. (e) Layer assembly, multiplexed sensing and treatment of a wireless stretchable biosensors. Reprinted with permission from [163]. Copyright (2023) American Association for the Advancement of Science.

Wound healing consists of three main stages including inflammatory, proliferative, and remodeling. Wound healing is a complex process that relies on the interaction of multiple factors [164]. During the healing process, unanticipated bacterial or fungal infections can significantly increase the difficulty and duration of

wound healing, and in severe cases can even lead to amputation or death. Although careful wound care can greatly reduce the possibility of bacterial infection [165], wound monitoring is still necessary to achieve the detection and intervention of bacterial infection at early stages due to the fear of serious consequences of wound infection. Currently, wound monitoring is mainly carried out by designated caregivers [166]. However, the relatively frequent removal of the dressing on the wound will not only increase the risk of infection of the wound exposed to the external environment, but also aggravate the pain of the patient and the burden of the caregiver. In fact, once a wound is infected by bacteria, the physiological indicators of its exudate will change significantly, such as a temperature increase, a decrease in pH, and additional bacterial secretions (uric acid) [167, 168]. Soft biosensors developed for continuous monitoring of wound exudate could be sensitive to detect bacterial infection in time. In addition, the healing cycle of chronic wounds exceeds three months, causing serve pain to the patient. Continuous monitoring of the exudate provides feedback on the healing status of chronic wounds. The pH of the exudate from a wound that is difficult to heal is usually between 7 ~ 9. When used in conjunction with the treatment of other diseases, certain medications, such as corticosteroids or other immunosuppressants, may inhibit wound healing by suppressing the immune response [169]. Inflammatory biomarkers include cytokines and chemokines that indicate the inflammatory phase of wound healing [170]. Elevated levels can signify chronic inflammation. Growth factors like platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) are essential for cell proliferation and tissue repair [171]. Monitoring biomarkers in wound healing can aid in early issue detection and personalized treatment. They assist healthcare professionals in assessing the progression of wounds and gaining a deeper understanding of the effectiveness of intervention measures. Pressure on wounds can lead to tissue damage and slow down the healing process. The flexibility and stretchability of biosensors can mimic soft wound tissue and minimize inflammation, qualifying for the long-time in situ biochemical analysis of wound.

Park's research group functionalized 3D porous laser-guided graphene (LGG) with 2D MXene nanosheets by dropping to enhance the electrochemical property and retain the high conductivity of 3D LGG [30]. After transferring the 3D LGG@2D MXene nanocomposite patterns onto the PDMS film, they further used specific uricase (UOx), pH-sensitive polyaniline (PANI) and thermosensitive effect of LGG-MXene/PDMS to construct the integrated biosensor for uric acid (UA), pH and temperature, respectively (**Figure 8**(a)). The sensitivity of UA biosensor is 422.5 $Ma \cdot mM^{-1} \cdot cm^{-2}$, ranging from 50 μM ~ 1 200 μM of UA. Oxygen is vital for promoting wound healing and resisting bacterial infections by increasing the proliferation of the fibroblasts and generating oxygen radicals [172]. Koh's research group further integrated oxygen, lactate, glucose, pH and temperature sensing components into a polyimide (PI) substrate with stretchable PDMS fibers and serpentine structure [29] (**Figure 8**(b)). This biosensor can withstand a 5% uniaxial strain (**Figure 8**(c)). The

oxygen sensor demonstrated rapid response to oxygen with a sensitivity of -28.3 Ma·cm^{-2} per mL·L^{-1} O_2.

For its unique characteristics such as superior flexibility, stretchability, self-healing and biocompatibility, hydrogel has become a promising candidate as medical wound dressing for biosensing and drug delivery [173-178]. Dehghani's research group combined pH-sensitive poly(styrenesulfonate) (PSS)-doped poly(3,4-ethylenedioxythiophene) (PEDOT) with hydrophilic polyurethane to prepare a soft hydrogel-based pH biosensor [179]. The pH responsiveness mainly originated from the change of conductivity based on ionic interaction between PEDOT and PSS. The electrical properties of this pH biosensor did not suffer any damage after being subjected to 400 extension cycles, which can monitor the pH changes between 3 ~ 13 stably. In addition to electrochemical methods, spectrometric principles were also used to fabricate pH biosensors with higher accuracy and sensitivity [180-182]. Ma's research group designed a flexible hydrogel-based pH biosensor based on pH-responsive fluorescence resonance energy transfer (FRET) between cyanine3 and cyanine5 [167]. The cleavage of cyanine5 in an acidic condition impacted the FRET effect. When the pH of the neutral solution decreased to 5.5, the ratio of the fluorescence intensity at 673 nm and 587 nm decreased gradually from 3.5 to 0.7 at 6 hours and remained stable. This demonstrates that pH reduction during wound infection can be monitored by measurement of fluorescence spectroscopy. This hydrogel-based pH biosensor also incorporated up-conversion nanoparticles and ultraviolet (UV)-cleavable polyprodrug to dispose of a controlled antibacterial drug release system for inhibiting wound infection. The recovery period of chronic wound exceeds three months [166]. The dressings used for chronic wounds are highly expected to be highly intelligent, which can integrate wound recognition, autonomous drug delivery and microenvironment monitoring to relieve the pressure of clinical care. Zhang's research group synthesized a multifunctional hydrogel dressing and realized an intelligent wound biosensor including identification, real-time monitoring and personalized management combined with the convolutional neural network (CNN) machine learning algorithm [162] (**Figure 8**(d)). Recently, Gao's research group reported a flexible, stretchable and biocompatible bioelectronic system, consisting of a mutimodal electrochemical biosensor array and non-invasive treatment platforms (**Figure 8**(e)) [142]. The serpentine and elastic SEBS increase the stretchability of the multiplexed sensor array patch. The sensitivities of glucose, lactate and UA sensors are 16.34 Na·mM^{-1}, 41.44 Na·mM^{-1}, and 189.60 Na·mM^{-1}, respectively. Combination therapy of controlled antimicrobial release and electrical stimulation of tissue regeneration can accelerate chronic wound healing. and controllably release antimicrobials.

3.3 Body fluid (intestinal fluid, saliva, and tear fluid) analysis

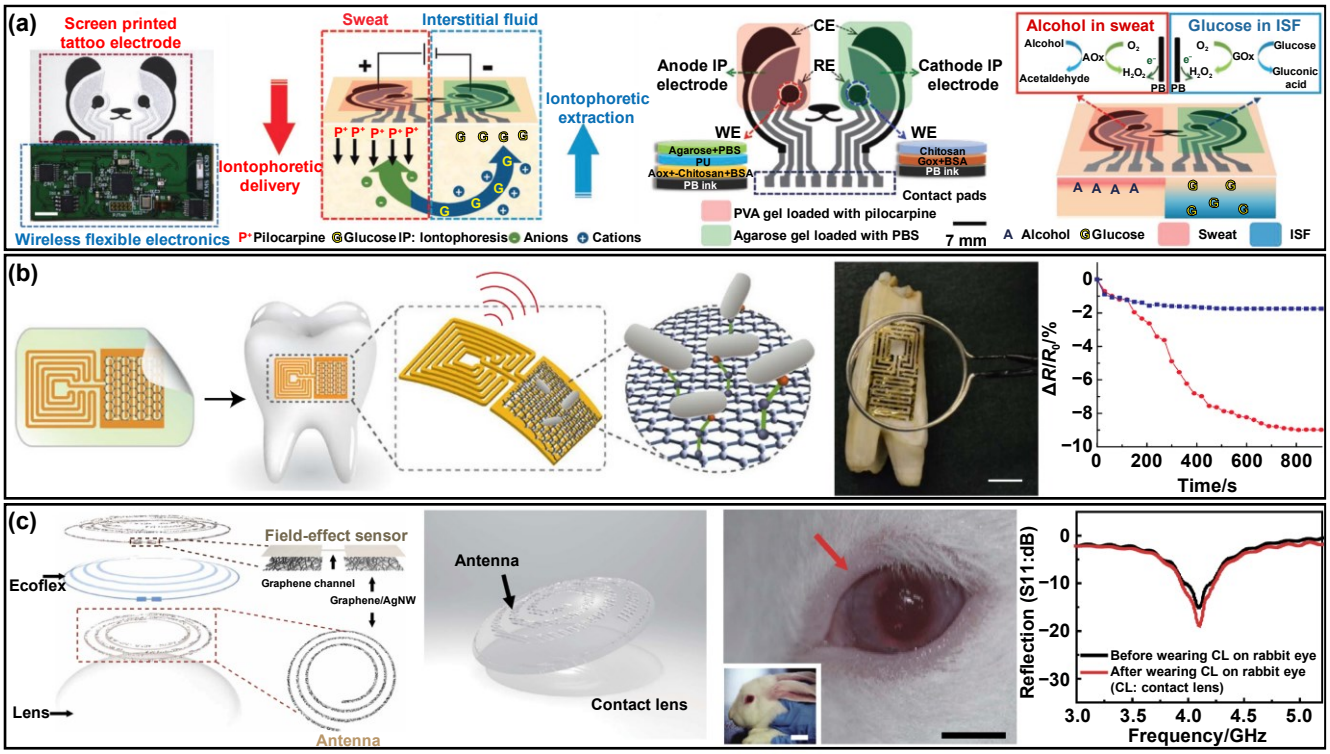

Figure 9. Soft biosensor for body fluid analysis. (a) Image and schematic representations of iontophoretic operation, glucohol biosensor, and biosensing operation of the screen-printed glucohol biosensor coupled with wireless flexible printed circuit board. [183] John Wiley & Sons. © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (b) Biotransferrable graphene wireless biosensor for bacterial sensing in human saliva. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nature Communications [184], © 2012. (c) Schematic of the wearable transparent glucose sensor on contact lens, photograph of wireless sensor integrated onto the eyes of a live rabbit, and wireless sensing curves of glucose concentration before and after wearing contact lens on an eye of live rabbit. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nature Communications [185], © 2017.

Body fluids, such as intestinal fluid, saliva, and tear fluid, contain rich biomarkers. These vital biomarkers include ions, small molecules (such as glucose, lactate, peptides), and proteins [186]. Precise and long-term sensing of these body fluids is crucial for unobtrusive monitoring and analysis of biochemical activities within the human body, with the potential to improve the management and treatment of chronic diseases such as diabetes, gout, and Parkinson's disease [187]. Stretchable and wearable biosensors, owing to their mechanical flexibility and deformability, can achieve accurate and long-term in-situ sensing of body fluids.

Interstitial fluid (ISF) is formed through capillary exchange during the blood flow process [188]. Monitoring biomarkers in ISF can provide more systematic and stable information compared to sweat monitoring, as the biomarkers in ISF originate from the blood and are highly sensitive to changes in local tissues [189]. Microneedle arrays can effectively penetrate the epidermis or upper layers of the dermis with minimal pain [190]. These microneedle arrays can be integrated with stretchable and wearable biosensors, serving as direct-measuring electrodes or collectors of ISF [191]. This integration enables minimally invasive sensing of biomarkers in ISF. For example, Wang's research group has outlined a wearable biosensor composed of pyramid-shaped microneedle structures integrated with Pt and Ag wires for minimally invasive

electrochemical monitoring of subcutaneous alcohol [192]. The microneedle aperture is modified by electropolymerizing o-phenylene diamine onto Pt wire microtransducer, followed by immobilizing alcohol oxidase (AOx) in the chitosan layer. The resulting microneedle-based enzyme electrode exhibited excellent selectivity, sensitivity (0.045 2 $nA \cdot mM^{-1}$), and stability (100 min) for alcohol detection in artificial ISF. Results from the ex vivo mouse skin model evaluations indicate that microneedle-based biosensors maintain stability and sensitivity for ISF analysis even after multiple skin penetrations. Similarly, their research team achieved simultaneous enzymatic-amperometric and nonenzymatic voltammetric analysis of levodopa by using square-wave voltammetry and chronoamperometry on both unmodified and tyrosinase-modified carbon-paste microneedle electrodes [193]. The design of this orthogonal wearable microneedle biosensor array offers a promising prospect for reliable, continuous, minimally invasive monitoring of levodopa in ISF, providing precise and effective treatment for Parkinson disease. Reverse iontophoresis is a technique that involves applying a potential difference across the skin, inducing an electro-osmotic flow of ions as charge carriers due to the inherent negative charge of human skin at physiological pH. Consequently, neutral molecules in ISF are transported to the outermost surface of the skin. Following this, in situ enzymatic electrochemical detection of the extracted biomarkers can be carried out on the skin using a wearable ISF sensor [194]. Wang's research team has developed a non-invasive blood glucose monitoring platform that combines amperometric biosensing with reverse iontophoresis, integrated into a temporary tattoo on the skin [195]. They designed an Ag/AgCl reverse iontophoresis electrode coated with agarose hydrogel to effectively transport ISF to the working and counter/reference electrodes. This flexible, cost-effective, and aesthetically pleasing iontophoretic biosensing temporary-tattoo based platform seamlessly conforms to human skin. Using a GOx-modified Prussian Blue transducer, selective amperometric biosensing can be achieved at low potentials. As shown in **Figure 9**(a), they further achieved simultaneous but independent sampling and analysis of two epidermal biofluids (ISF and sweat) in a single device [183]. This dual-sampling and detection epidermal system was realized by parallelly operating reverse iontophoresis to extract ISF from the skin and iontophoretically deliver a sweat-inducing drug into the skin. This wearable system was manufactured on an epidermal temporary tattoo platform using cost-effective screen-printing techniques for disposable use. Flexible circuit boards, magnetically attached to the tattoo, drove the iontophoretic electrodes, controlled the biosensors, and wirelessly transmitted the sensed information to a smartphone for real-time self-monitoring applications. The successful simultaneous on-demand sampling and analysis of ISF and sweat on a single wearable device expand the capabilities and scope of non-invasive epidermal biomarker biosensors.

Saliva contains various biomarkers such as microorganisms, antibodies, DNA, RNA, metabolites, lipids, and proteins, making it an ideal body fluid for monitoring human health [196]. Due to the ease of saliva

collection and its strong correlation with blood analytes, it has been extensively investigated as a potential source for non-invasive monitoring and diagnostics [197]. McAlpine's research group has proposed a novel approach by interfacing passive, wireless graphene biosensors to tooth enamel via silk bioresorption (**Figure 9**(b)) [184]. Initially, the graphene biosensors are printed onto the thin-film substrate, and then the electrode is patterned through inductive coil antennas, allowing graphene to make contact with the interdigitated electrodes. Ultimately, the graphene/electrode/silk hybrid structure is transferred onto dental enamel. Achieving bioselective detection of bacteria at the single-cell level is accomplished by self-assembling antimicrobial peptides onto graphene. This device structure exhibits exceptionally high chemical and biological sensing sensitivity, with detection limits reaching single bacteria, while concurrently achieving wireless remote powering and readout. Uric acid is another crucial health biomarker due to its association with various conditions such as hyperuricemia, kidney syndrome, and gout. Wang's research team has integrated a uricase-modified screen printed electrode system into a mouthguard platform, along with anatomically-miniaturized instrumentation electronics featuring a potentiostat, microcontroller, and a Bluetooth Low Energy transceiver [198]. This wearable electrochemical biosensor demonstrates the ability to non-invasively monitor uric acid levels in saliva, exhibiting high sensitivity (2.32 $Ma \cdot mM^{-1}$), selectivity, and stability.

Tears are intimately connected to blood as plasma continuously permeates into tears through the blood-tear barrier [199]. The human eye, being more delicate than the skin, is also more sensitive to pain. Therefore, the requirements for materials and manufacturing techniques are more stringent when it comes to biosensors for the continuous monitoring of tear fluid on the corneal surface [194]. Contact lenses, being the most common ocular platform, naturally interact with the cornea in a non-invasive manner. They serve as a potential platform for constructing soft sensors to monitor tear biomarkers safely and reliably. Park's research team has devised a stretchable biosensor based on wearable soft contact lenses for highly sensitive wireless glucose detection (**Figure 9**(c)) [185]. The combination of graphene and metal nanowires imparts excellent transparency (> 91%) and stretchability (≈ 25%) to the sensor, enhancing its flexibility. Glucose sensing is achieved through a field-effect transistor (FET) array, where the graphene-based channel, utilizing pyrene linkers immobilized with GOx through π–π stacking, and the source/drain electrodes based on silver nanowires are passivated with epoxy layer. Graphene-AgNW electrodes and graphene channels are patterned by photolithography on an ultra-thin poly(p-xylylene) substrate (thickness: 500 nm). All components of the device are transparent, featuring faintly visible spiral antennas, and conformally wrapping around the curvature of the contact lens. Despite the presence of interferents in tears, the sensor exhibits a specific response to glucose. After a feeding period of 2 hours, the contact lens sensor detected an increase in rabbit glucose concentration. Furthermore, the sensor maintains stability during extended wear for up to five hours,

including repeated blinking periods. Furthermore, Hahn's research team has developed a smart electrochemical contact lens that integrates a glucose biosensor with wireless power and remote communication systems [200]. The eye-specific glucose biosensor, uniformly coated and anchored in chitosan and poly(vinyl alcohol)-bovine serum albumin cross-linked hydrogel, exhibits high sensitivity, linearity, and stability upon repeated applications over 63 days of long-term storage. This sensor enables real-time biosensing of glucose concentrations in tears and on-demand therapeutic drug delivery of quercetin. The ongoing advancement of soft biosensors based on contact lenses holds the promise of meeting the preventive, diagnostic, and therapeutic needs for various ocular and other diseases. In addition to the contact lens-shaped tear fluid sensor, Wilson’s research group has also developed a flexible sensor named NovioSense, designed to be placed in the fornix of the lower eyelid to monitor changes in glucose levels during the basal tear flow period [201]. The device consists of a flexible coil formed by multiple wires (electrodes) wound in parallel, creating a spring-shaped ampere-hour battery measuring 15 mm in length and 1.3 mm in diameter. These wires are made of uncoated platinum/iridium (Pt/Ir, 90/10) and stainless steel coated with 10 μm polyethylene terephthalate, serving as isolators and spacers. This coil-shaped design enhances the flexibility of the device and serves as a platform for wireless power and data transmission. The introduction of a hydrophilic and biocompatible polysaccharide hydrogel protective coating further enhances the comfort of wearing. This coating also incorporates immobilized GOx as a sensing element, enabling linear detection of glucose within the concentration range of 0.1 mM ~ 1 mM.

4. Manufacturing and Applications of Implantable Biosensors

The non-invasive in situ analysis of cutaneous exudate by soft wearable sensors can monitor the human body's health status. However, many important biomolecules such as neurotransmitters and nucleic acid biomarkers are almost absent in non-invasive biological fluids, which makes it difficult for wearable sensors to reveal the underlying mechanisms of life activities. Soft implantable biosensors can accommodate the micro-movements of biological tissue, reduce inflammation, and thus improve the sensing performance during long-term implantation. The design and optimization of soft implantable chemical biosensor devices are expected to deepen our understanding of life activities and complex diseases.

4.1 Brain neurotransmitter sensor

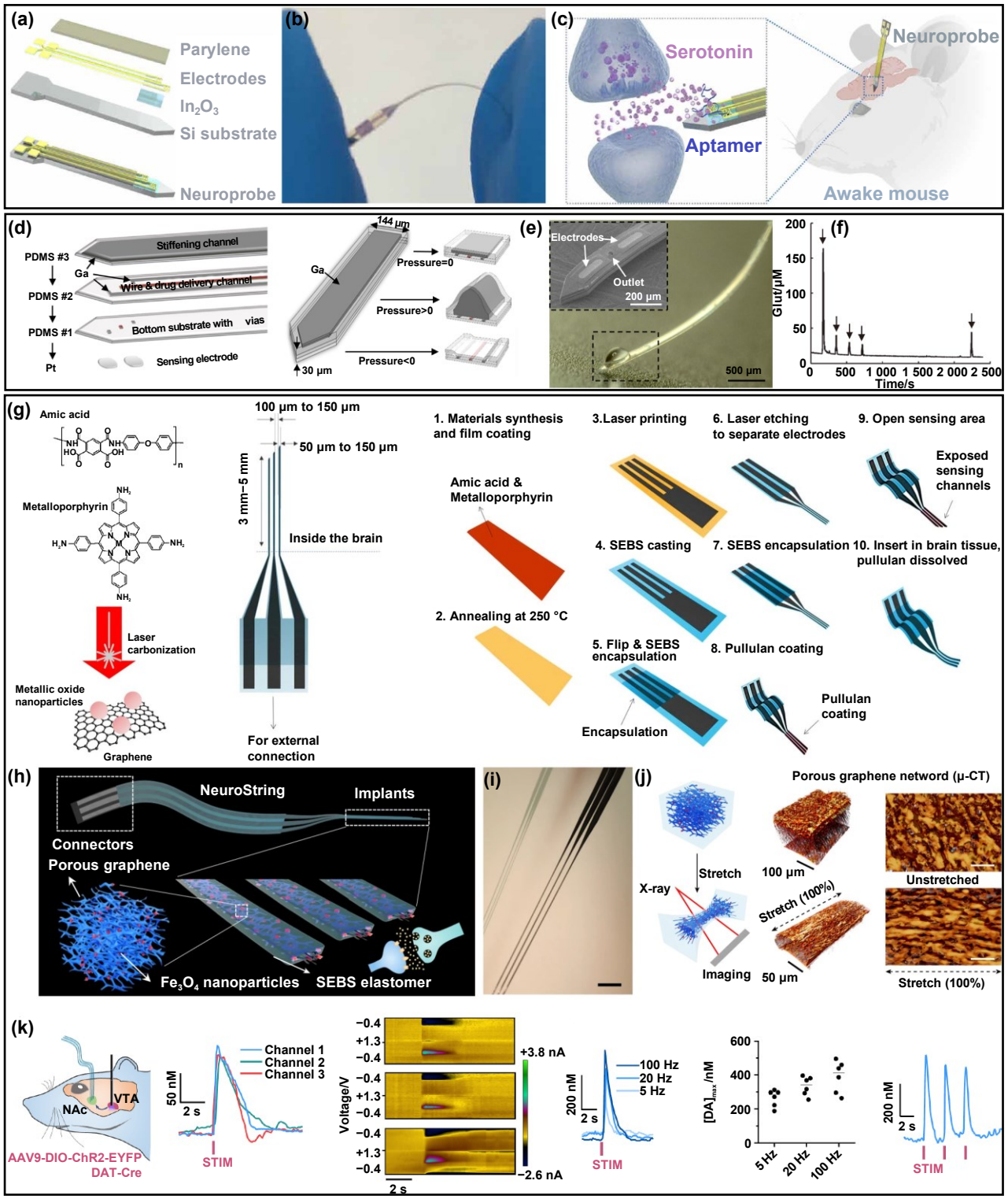

Figure 10. Soft brain neurotransmitter sensor. Schematic illustration of (a) implantable aptamer-field-effect transistor (FET) neuroprobe and (b) corresponding serotonin neurotransmitter monitoring. (c) Photograph displaying the FET neuroprobe can be bent. Reprinted with permission from [27]. Copyright (2021) American Association for the Advancement of Science. (d) Schematic illustration of design mechanism of flexible liquid metal neural probe. (e) A liquid metal probe in the soft state with integrated drug delivery function. (f) In vivo detection of glutamate by liquid metal neural probe. Reprinted from [26], Copyright (2019), with permission from Elsevier. (g) Schematic of the fabrication of the NeuroString sensors. (h) Schematic of the implantable NeuroString biosensor. (i) A stretched three-channel NeuroString with each channel for sensing brain neurotransmitters separately. Scale bar: 3 mm. (j) Schematic, X-ray tomography 3D reconstruction and tomography of graphene nanofiber. (k) Neurochemical sensing in the brain. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nature [24], © 2022.

The brain is the main part of the central nervous system that precisely regulates life processes by controlling the release of a diverse range of neurotransmitters. For example, Endogenous serotonin has profound effects on the regulation of the immune system [202], the formation of biomembrane [203] and the development of fetal neurons [204]. Dopamine is involved in the control of almost all higher-level actions such as cognitive processes [205]. Acetylcholine can control the attentional processes [206]. The perturbation of the levels of these neurotransmitters is directly associated with various diseases such as Alzheimer's disease (AD), Dementia with Lewy bodies (DLB), Parkinson's disease, etc. Long-term monitoring of the secretion of specific neurotransmitters in the brain is necessary to establish a causal relationship among biochemical processes, consciousness and behavior, which will also help to advance the research process for pathogenesis, prevention and precise treatment of neurological diseases[207, 208]. Soft implantable chemical biosensors can achieve in-situ dynamic monitoring of neurotransmitters in the brain while maximizing the avoidance of inflammation and thrombosis induced by long-term implantation.

Silicon-based neuroprobes are becoming a highly sought-after and effective implantable device for the detection of brain neurotransmitters due to their high spatial and temporal resolution [209]. However, silicon-based materials are usually rigid and brittle [208], and when implanted are likely to cause brain scarring at the site of the wound, thus impeding the efficient transmission of neurotransmitter sensing signals [210]. To increase the flexibility of silicon-based neural probes, Andrews's research group reduced the thickness and width of Si neuroprobe to 50 μm (**Figure 10**(a)) [27], enabling the Si neuroprobe with reduced size can be easily bent (**Figure 10**(b)). Meanwhile, the stiffness of as-prepared Si neuroprobe was still enough to penetrate a nitrile glove. The surface of neuroprobe was modified with serotonin aptamers to specifically detect serotonin in vivo (**Figure 10**(c)). However, the Young's moduli of Si neuroprobe (~150 Gpa) and brain neural tissue (~1 kPa ~ 10 kPa) are markedly mismatched [210, 211], which may induce immunological responses for long-time implants [212]. Chiou's research group injected gallium (Ga) liquid metal into the PDMS channel to fabricate a chemical sensor with convertible stiffness based on the solid/liquid phase transition of metal Ga (**Figure 10**(d)) [26]. Under cooled conditions, the probe was rigid enough to be inserted into the brain. When the ambient temperature raised to the body temperature (**Figure 10**(e)), the metal Ga in the PMDS channel melted and the originally hard probe became flexible. Glutamate oxidase (GlutOx)-coated Pt microelectrodes on the flexible probe realized in vivo electrochemical sensing of glutamate by cascade catalytic reaction of glutamate and hydrogen peroxide (**Figure 10**(f)). The sensitivity, LOD and response time of this Ga liquid metal probe are about 8.2 $Pa{\cdot}\mu M^{-1}$, 0.39 μM and 1 s, which are comparable to those of the Si probe previously reported [213, 214]. Although these two ingenious designs endowed the neuroprobe with flexibility, the design of a truly stretchable biosensor for real-time monitoring of biochemical signaling in the

brain is still extremely challenging. Bao's research group developed a soft and stretchable neurotransmitter biosensor called NeuroString [24]. The fabrication process was shown in **Figure 10**(g). This NeuroString was mainly composed of graphene as electrode material and Fe_3O_4 nanoparticles as a catalytic agent. To improve the crack of graphene under strain, they also used polystyrene-block-poly(ethylene-ran-butylene)-block-polystyrene (SEBS) elastomer as the matrix to coat the graphene nanofiber networks with Fe_3O_4 nanoparticles (**Figure 10**(h)). **Figure 10**(i) exhibits that the NeuroString was soft, elastic, thin and long strings to reduce brain tissue damage during implantation. When the graphene-SEBS composite was stretched to 100% strain, the interconnected 3D network structure became aligned, conducing to maintain conductivity (**Figure 10**(j)). The sheet resistance increased <200% under 50% strain. This NeuroString could dynamically detect dopamine concentration with sub-second temporal resolution in the mouse brain (**Figure 10**(k)). Immunohistology indicates that after 16 weeks of implantation, the soft NeuroString exhibits superior biocompatibility compared to traditional rigid probes, with fewer adverse tissue reactions.

The brain is an extremely sensitive and delicate organ, so any adverse reactions can have serious consequences. The long-term use of implantable biosensors within the brain presents critical safety and biocompatibility considerations. To address these concerns, researchers and engineers have developed materials and design considerations aimed at improving biocompatibility and safety. First, material selection is crucial. Implantable biosensors must be constructed from biocompatible materials to ensure they do not trigger immune responses or tissue rejection [215]. Commonly used materials include medical-grade silicone, conductive polymers, and conductive hydrogels, as they are compatible with neural tissues [110, 216, 217]. Additionally, implantable biosensors must possess sufficient mechanical flexibility to conform to the brain's anatomical structure, reducing damage and irritation to surrounding tissues [210]. Minimizing implantation damage can be achieved through strategies such as reducing the size of the implant and optimizing insertion methods [218, 219]. Reducing inflammation and immune reactions is also of paramount importance. As these initial reactions take place on the surface of the implant, surface modification stands out as an intuitive strategy for controlling the inflammatory response. This can be achieved through specialized coatings or encapsulation that minimizes immune responses [220]. Some neural detectors may be designed to release anti-inflammatory drugs to further reduce inflammation or scar tissue formation [221].

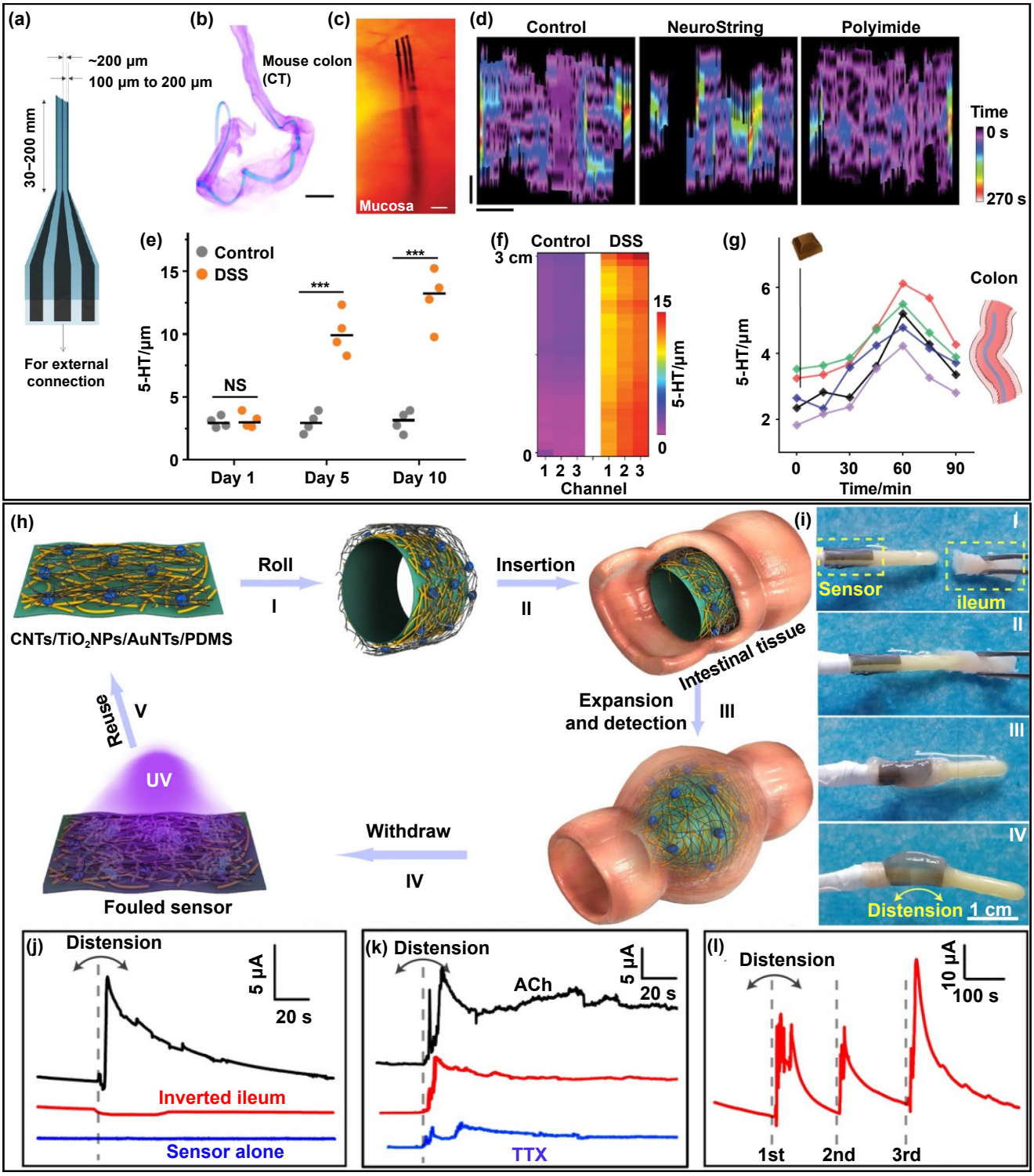

Figure 11. Soft gut neurotransmitter sensor. (a) Layout of the NeuroString electrode for gut neurotransmitter sensing. (b) Ex vivo X-ray CT image of a gut NeuroString placed in the mouse colon. Scale bar: 5 mm. (c) Ex vivo image showing that the NeuroString can conform to the mucosa of mouse colon. Scale bar: 1 mm. (d) Representative spatiotemporal maps of the CMMC. (e) Mouse colon 5-HT concentration change measured by NeuroString biosensor. (f) Representative 5-HT concentration mapping of the mouse colon (3 cm from the anus) of a colitis mouse and a healthy mouse. (g) 5-HT level changes in the colon using chocolate as stimulation for mice. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nature [24], © 2022. (h) Schematic of stretchable CNTs/TiO_2NPs/AuNTs biosensor for implantable monitoring 5-HT in intestine. (i) A photograph showing the CNTs/TiO_2NPs/AuNTs electrode inserted into the lumen of a segment of ileum tissue (I-III) and the extension state of the sensor and ileum after the catheter balloon was filled with water (IV). (j)-(l) Current responses detected from normal ileum tissue

submitted to mechanical distension stimulation. [28] John Wiley & Sons. © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Intestine is an important digestive organ, providing energy for life movement. At the same time, a large number of immune cells and inflammatory proteins are gathered and produced in the intestine. Maintaining intestinal health is essential for human health. As the forefront of the human immune system, the intestine is relatively fragile and vulnerable to attack by pathogenic factors in vitro, resulting in a variety of intestinal diseases, such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), necrotizing enterocolitis (NEC), cryptosporidiosis, etc [222-225]. The precise diagnosis and treatment of intestinal diseases are extremely important but challenging due to the complexity of the intestinal system. To date, a large number of biomarkers have been found and identified to be closely associated with intestinal diseases including peptides, proteins, antibodies, microbial products and microbes [3, 4, 226]. Although some intestinal biomarkers have been used as clinical diagnostics, the current detection of intestinal biomarkers is mainly based on fecal assays [226]. Research into the impact of *in situ* biomarkers in the gut on intestinal health is far from ideal due to the lack of suitable gut biosensors. The development of soft chemical biosensors promises to enable real-time *in vivo* detection of intestinal markers. In addition, the soft chemical biosensors can keep conforming to the soft, long and twisting intestinal mucosa, for *in situ* high-fidelity detection of the changes of signal molecules of the intestinal tract when withstanding different mechanical forces such as stretching/contraction and flow shearing force [227].

Serotonin is recognized as a representative gut marker and signaling molecule, and fluctuations in its levels can reflect changes in gut motility and health [228, 229]. Fortunately, the NeuroString for brain neurotransmitter sensing introduced in the previous section has a widespread universality [24]. Simply adjusting the laser printing and cutting parameters can make the rope have enough length (**Figure 11**(a)) to meet the needs of intestinal implantation without catheter support (**Figure 11**(b)). Due to its excellent stretchability, the NeuroString can perfectly conform to the colon mucosa through hydrophobic interaction after implantation (**Figure 11**(c)). Compared with flexible polyimide fiber without stretchability, the implantation of the NeuroString did not delay colonic migrating motor complexes and slow-wave-induced contractions (**Figure 11**(d)) and induced obvious tissue damage, showing the better biocompatibility of the stretchable NeuroString. The NeuroString was further used to detect concentration (**Figure 11**(e)) and map the spatial distribution (**Figure 11**(f)) of serotonin in colon. Serotonin concentration in colon of mice with acute enteritis was significantly higher than that of healthy mice. In addition, chocolate feeding also led to an increase in serotonin content in the colon of mice (**Figure 11**(g)). This NeuroString cooperating with various recognition elements has great potential to be extended to the dynamic detection of other biomarkers in the gut. Huang's research group designed and fabricated a stretchable electrochemical biosensor for ex vivo

detecting the serotonin release induced by mechanical distension of intestine [28]. This stretchable biosensor possessed a sandwich structure consisting of underlying gold nanotubes (AuNTs) as an electrode, intermediate layered TiO_2 nanoparticles (TiO_2NPs) as photocatalytic cleanser and CNTs as an external protective layer (**Figure 11**(h)). Cyclic voltammograms showed that the peak current of CNTs/TiO_2NPs/AuNTs electrode persisted over 90% under 50% strain, confirming the excellent electrochemical stability. The LOD was calculated to be 10 nM by amperometric measurements, which was significantly lower than the content of serotonin around intestinal mucosa by 4 orders of magnitude [230]. To achieve implantable serotonin detection, they inserted a balloon catheter coiled by CNTs/TiO_2NPs/AuNTs electrode into the rat ileum segment. Intestinal distension was caused by balloon inflation (**Figure 11**(i)). **Figure 11**(j)-(l) demonstrated that the distension of the ileum could elevate the endogenous release of serotonin. The CNTs/TiO_2NPs/AuNTs stretchable electrodes can effectively resist the adhesion of biomolecules to achieve the ex vivo sensitive detection of serotonin in the intestine segment. However, due to its planar structure based on the PDMS matrix and limited length, it is difficult to actually implant the slender intestinal tissue in vivo without a catheter support.

Maintaining homeostatic pH regulation is crucial for sustaining proper cellular and physiological functions. For instance, leakage of gastrointestinal fluids secondary to anastomotic surgery can lead to significant alterations in local pH equilibrium, potentially propagating throughout the peritoneal cavity and causing organ dysfunction and failure. Therefore, precise monitoring of pH variation in tissues surrounding an anastomosis can mitigate postoperative complications in gastrointestinal surgery. For example, Rogers's research group developed bioresorbable shape-adaptive structures that enable rapid, noninvasive measurements of homeostasis in deep tissues by conventional ultrasound imaging techniques [231]. The pH responses of the hydrogels originate from their chemical compositions. The protonation of tertiary amine moieties or carboxyl moieties results in a corresponding conformational change of the hydrogel network as the pH decreases or increases, respectively. The expansion of responsive hydrogel-based thin films induced by pH perturbations leads to changes in the separation of sparse metal elemental assemblies. The significant mismatch in acoustic impedance between these elements and the surrounding materials generates high contrast in ultrasound images, allowing for precise measurement of their separations and thus accurate assessment of local pH changes in the gastric, small intestinal, and pancreatic tissue. At body temperature, the devices largely dissolve within 174~241 days, indicating their bioresorbable property.

5. Conclusions and perspectives

In less than a decade, people have been fortunate to witness significant progress in the field of soft biochemical biosensors. Soft wearable chemical biosensors can realize the quantitative analysis of human sweat and wound exudate to monitor human health. Soft implantable chemical biosensors can detect the concentration of chemical substances in living tissues and organs in situ, which is of great significance in deeply revealing the internal relationship between the fluctuation of detected substances and physiological activities and health status. **Table 2** summarizes the material-fabrication-application-performance relationship of soft electronics for in situ biochemical sensing. It is expected that the continuous progress of soft chemical biosensor technology will seek greater benefits for human health. However, there remain some limitations and challenges (**Figure 12**).

Table 2. Material-fabrication-application-performance relationship of soft Electronics for in situ biochemical sensing.

Application	Substrate	Material	Structure	Fabrication method	Stretchability	Functionalization	Modification method	Targeted species	Sensitivity	Detection Limitation	Ref.
Sweat	SEBS/AuNWs	Au	Wrinkle	Dry Spinning Pre-strain Electroless plating	200%	GOx	Drop-casting	Glucose	11.7 μA mM^{-1} cm^{-2}	6 μM	[31]
	PDMS	Silver	Nanowire	All-printing	50%	GOx Graphene oxide PANi	Drop-casting Electrochemical deposition	Glucose Na^+ K^+ H^+	0.714 nA μM^{-1} 60.1 mV per decade 64.5 mV per decade 60.0 mV per decade		[32]
	PDMS	Au and C	Nanotube	Vacuum filtration	30%	$CoWO_4$	Dipping	Glucose pH	10.89μA mM^{-1} cm^{-2} 71.44 mV pH^{-1}	1.3 μM	[33]
	EcoFlex	Au and Polyimide-coated copper	Island–serpentine bridge	Lithographic technique	75%	CNT	Screen printing	Catecholamine Glucose Nucleic acids Lactate			[51]
	PDMS	Au and graphene	Mesh serpentine	Chemical vapor deposition	30%	PANI Gox	Electrodeposition Drop-casting	pH Glucose			[134]
	SEBS	CNT	Wrinkled	Pre-strain CVD	60%	Cu	Magnetron sputter deposition	Glucose	46 mA M^{-1}	0.05 mM	[150]
	PDMS	Au	Mogul-patterned	Thermal deposition	30%	Nanoporous gold	Electrodeposition	Glucose	253.4 μA cm^{-2} mM^{-1}		[133]
	PDMS	Au	Mogul-patterned	Thermal deposition	30%	3D-nanostructured gold	Electrodeposition Drop-casting	Cortisol	0.273 Ohm ng^{-1} mL^{-1}		[29]
	PDMS	rGO/PU		Injection	20%	Ni-Co MOF	Drop-casting	Glucose	425.9 μA mM^{-1} cm^{-2}	3.28 μM	[146]
	SEBS/AuNWs	Au	Wrinkled	Pre-strain Electroless plating	100%	LOx	Drop-casting	Lactate	19.13 μA mM^{-1} cm^{-2}	0.137 mM	[30]
	Textile	CNT RGO		Immersion	50%	GOx	Drop-casting	Glucose	3.87 μW cm^{-2} mM^{-1}	3.95 μM	[117]
	Ecoflex	CNT PANI	Wrinkled	Pre-strain Spraying	200%	GOx LOx Creatininase/crertinase/sarcosine oxidases	Drop-casting	Glucose Lactic acid creatinine			[28]
Wound	PDMS	Graphene MXene	3D porous Nanosheet	CO2 Laser Drop-casting		UOx PANI	Layer-by-layer	Uric acid pH	422.5 μA mM^{-1} cm^{-2} -57.03 mV pH^{-1}	50 μM	[27]
	PDMS	Au	Serpentine	Electron beam evaporation		Poly(vinyl chloride) Nafion LOx GOx	Drop-casting	pH Oxygen Lactate Glucose	-55.0 mV per decade -28.3 μA cm^{-2} per mL L^{-1} O_2 -0.24 μA mM^{-1} cm^{-2} -2.98 μA mM^{-1} cm^{-2}		[26]
Brain	PDMS	Ga	Liquid metal	Injection		GlutOx	Drop-casting	Glutamate	8.2 pA μM^{-1}	0.39 μM	[24]
	SEBS	Graphene	Porous	Laser carbonization	50%	Fe_3O_4 NPs	Laser carbonization	Dopamine Norepinephrine Serotonin Epinephrine		5.6 nM 7.2 nM 3.5 nM 6.6 nM	[32]
Gut											
	PDMS	Au	Nanotube	Galvanic displacement	50%	TiO_2 NPs	Electrophoretic deposition	Serotonin		10 nM	[215]

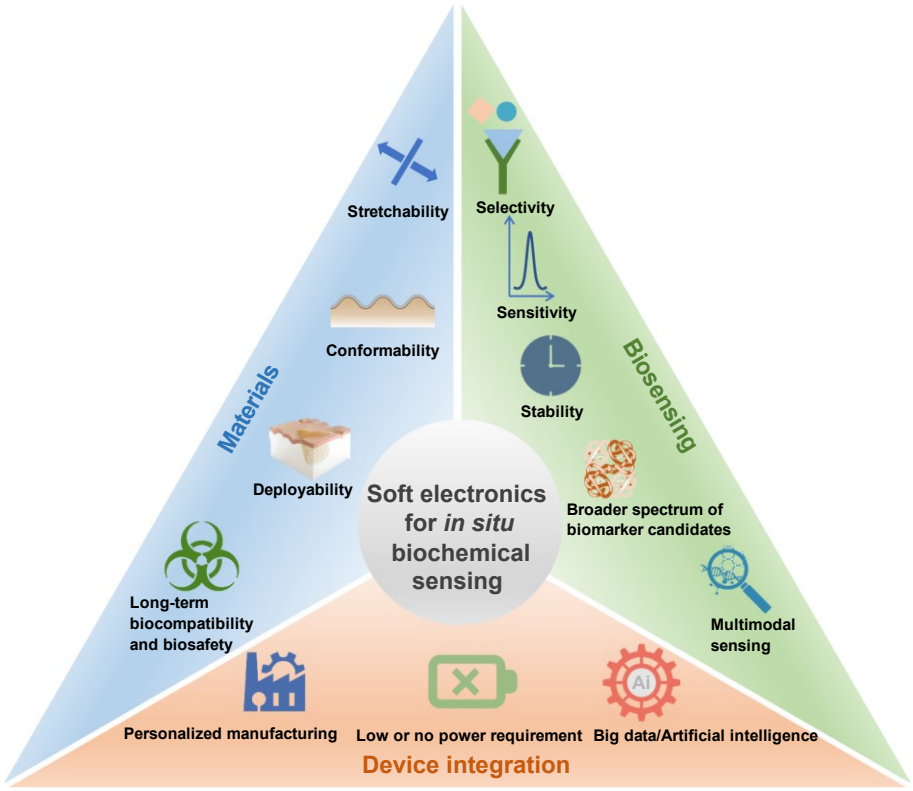

Figure 12. Key requirements and challenges of soft electronics for in situ biochemical sensing.

In the context of sweat analysis, various enzymes have been employed to modify working electrodes for the specific detection of glucose, lactic acid, or cortisol. The challenge lies in maintaining enzyme activity, prompting exploration into non-enzyme working electrodes using novel nanomaterials with high catalytic activity. However, these materials demand further optimization and investigation into their selectivity, sensitivity, and biosafety when in contact with human skin. While stretchable electrodes offer skin conformity, practical applications often necessitate external electrochemical workstations, limiting the wearer's freedom of movement. Improving the power density of self-powered systems utilizing chemical energy in sweat is essential. Integration challenges, such as stretchable electrode arrays, circuit boards, and energy sources, warrant heightened attention. Components like wireless power transmission and batteries must be stretched and miniaturized for seamless biosensor system integration [232].

The principles guiding wound monitoring mirror those of sweat analysis, but soft wound biosensors, in direct contact with wound surfaces, demand heightened security and conformity compared to sweat biosensors. The complexity and diversity of wound shapes, areas, and trauma levels pose challenges. Overcoming this requires personalized fabrication, with computer scanning, modeling, and 3D printing emerging as effective tools. The ideal wound biosensor envisions two components: disposable smart dressings for on-site, individualized monitoring and treatment, and a reusable device integrating standardized components for data collection, analysis, and transmission.

In the future, another opportunity lies in the development of soft wearable multimodal biochemical sensors integrated with artificial intelligence and/or machine learning tools to learn from collected extensive data and achieve advanced subsequent analytical capabilities. By integrating multimodal sensors, a more comprehensive dataset covering multiple physiological and health parameters can be obtained. With the assistance of artificial intelligence and machine learning tools, the system can extract patterns, trends, and correlations from this vast data, providing deeper insights for personalized healthcare and treatment. This integration also facilitates real-time monitoring and prediction, enabling healthcare teams to detect potential health issues earlier and take appropriate actions. Moreover, conducting extensive clinical trials across different age groups and diagnoses can validate the applicability and effectiveness of these soft wearable sensors in diverse populations. The results of these trials will contribute to further refining the design and functionality of the sensors to meet the specific needs of different patient groups. Additionally, validating efficacy and performance will enhance the medical community's confidence in these innovative technologies, promoting their broader application in the healthcare field.

The design and fabrication of soft implantable chemical biosensors present even greater challenges compared to their wearable counterparts. In vivo implantation necessitates superior conformability, demanding not only biocompatibility and biosafety but also non-interference with neurotransmitter and biomarker expression. Current efforts in soft implantable chemical biosensors focus on limited designs for brain and gut sensing. Extensive research is needed to develop stretchable electrodes and recognition elements for broader neurotransmitter detection, especially in monitoring complex conditions like intestinal microbiota changes. Achieving high selectivity and anti-adhesive properties is challenging in the complex fluid composition of the brain and intestine. Multi-channel soft implantable chemical biosensors capable of simultaneous detection of multiple biosignaling molecules are crucial for understanding synergistic regulatory mechanisms. Once highly integrated, the focus will shift to fixation technology and comfort optimization for long-term independent implantation, blurring the boundary between wearable and implantable devices.

While there are currently significant differences between wearable and implantable biochemical sensors, both fall under the umbrella of soft electronics. In the future, significant progress can still be achieved collaboratively in materials and manufacturing technologies. Continuous improvement in flexibility, stretchability, sensitivity, selectivity, stability, and safety is essential for the development and optimization of sensors in both categories. There are many challenges as well as opportunities in terms of manufacturing soft electronics for biochemical sensing. Increasing the resolution of the biosensing electrodes is essential to probe the local dynamics of physiological states, thus providing meaningful information in understanding cell communication, cell-microbe communication, and neuronal circuits. In addition, using microfabrication to reduce the dimension of the microelectrodes can further reduce the device’s bending stiffness, thus

significantly increasing the device's mechanical compliance when interfacing with soft and moving tissue. The cleanroom photolithography patterning process is conventionally used in the microfabrication of silicon and metallic materials. However, because of their limited catalytic properties, silicon or metallic electrodes are not favored for biomolecular sensing, while new approaches to process unconventional carbon-based materials and polymeric materials are desired. Furthermore, the materials used in metallization or encapsulation are usually inorganic materials with extremely high modulus, which cannot meet the requirement of high softness and stretchability. Overall, new soft sensing materials and encapsulation materials that can be photopatterned must be explored to ensure the mechanical compliance of the electrode array when interfacing with intestinal tissue. To achieve this, unconventional materials processing approaches will need to be developed. Beyond photolithography, new solution-processable or printing methods will need to be developed to allow large-area fabrication of the soft sensors, which might integrate inorganic materials, polymers, as well as biological enzymes in a single system. Such large-area fabrication will not only improve the manufacturing capacity of the soft sensors but will also lead to large-area devices that can cover a large body area that is difficult to cover with a single wafer. Meanwhile, besides seamless integration with the biological system, these soft biosensing electronics will also need to be seamlessly integrated with wireless electronics and computers, or even localized amplifiers, so that the maximum power of modern computer devices and artificial intelligence goes beyond Moore's law.

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