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REVIEW ARTICLE

Flexible biochemical sensors for point-of-care management of diseases: a review

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Abstract

Health problems have been widely concerned by all mankind. Real-time monitoring of disease-related biomarkers can feedback the physiological status of human body in time, which is very helpful to the diseases management of healthcare. However, conventional non-flexible/rigid biochemical sensors possess low fit and comfort with the human body, hence hindering the accurate and comfortable long-time health monitoring. Flexible and stretchable materials make it possible for sensors to be continuously attached to the human body with good fit, and more precise and higher quality results can be obtained. Thus, tremendous attention has been paid to flexible biochemical sensors in point-of-care (POC) for real-time monitoring the entire disease process. Here, recent progress on flexible biochemical sensors for management of various diseases, focusing on chronic and communicable diseases, is reviewed, and the detection principle and performance of these flexible biochemical sensors are discussed. Finally, some directions and challenges are proposed for further development of flexible biochemical sensors.

Keywords Disease management · Flexible biochemical sensor · Healthcare · Point-of-care · Real-time monitoring

Introduction

For thousands of years, health problems have been always plaguing human beings; for example, diseases often cause people's anxiety, pain, and even disability, which seriously affects daily life [1]. Conventional treatment or medical intervention is usually carried out after medical examination, such as blood/urine/stool routine test and medical imaging, only when serious symptoms appear, which might miss the optimal opportunity for treatment and meanwhile consume central medical resources and specialized manpower. Therefore, early diagnosis and treatment can significantly increase the overall survival rate and improve the prognosis, which might be one of the most cost-efficient approaches to release the global or individual burden. A more important fact is that, health monitoring during the entire process from or even before the onset of a disease to its cure urgently required advances in point-of-care testing (POCT), which can provide timely physiological information for treatment strategies. However, existing commonly used in vitro small or wearable non-flexible/rigid biochemical sensors have low fit and comfort with the human body [2, 3], leading to low accuracy for detection and discomfort for users in long-term wearing, which hinders the real-time health monitoring.

With the progress of material science and ultrathin film fabrication technologies [4], sensors based on flexible and stretchable materials have been explored for human healthcare monitoring [5–7]. Compared with the traditional non-flexible/rigid sensors, the shape adaptability of flexible sensors makes it easier to capture the target analytes, thus generating higher quality signals. Furthermore, it is worth confirming that the good fit between flexible sensors and human body can better meet the needs of long-term point-of-care (POC) monitoring. Thereinto, the rapidly growing demand for real-time monitoring of disease-related biomarkers in vivo or on skin has attracted tremendous efforts

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into the design and construction of flexible biochemical sensor devices with high performance, which are mainly composed of flexible substrates, biochemical receptors, and active elements [1, 8].

The substrate providing solid support for sensors is the main source of stretchability and flexibility, which directly determines the comfort level and long-term reliability when applied to the human body [1, 9]. Some synthetic polymers, such as polydimethylsiloxane (PDMS), polyethylene terephthalate (PET), polyimide (PI), polyethylene naphthalate (PEN), and hydrogels, have been well studied as flexible substrates for sensing platforms [10, 11]. Paper [12], textiles, and fibers [13, 14] centered great expectations as flexible substrates for their obvious advantages, such as flexibility, light weight, portability, low cost, and durability. Thin metallic foils can also be used as useful flexible substrates with superior conductivity. Moreover, a variety of naturally derived biomaterial, such as silk proteins, polysaccharides, and gelatins, have been proposed as substrates for flexible sensors, due to their biocompatibility and biodegradability [15]. Like non-flexible/rigid biochemical sensors, the receptors of flexible biochemical sensors mainly include enzymes, antibodies, aptamers, polysaccharides, and cells, which are used for sensing disease-related biomarkers. In order to ensure stable function and longevity of biochemical receptors, flexible substrates generally need to be functionally modified to provide appropriate attachment and fixation [16]. After biochemical sensing, active elements are used to convert the biological interaction into a readable or processable electronic signal. Conducting polymers [17], metals [18], carbon-based nanomaterials [19], and optical elements [20] have been used to manufacture active elements. Flexible biosensors can be customized for both implantable and wearable applications. Implantable flexible sensors in vivo detect biomarkers in blood, interstitial fluid (ISF), cerebrospinal fluid (CSF), etc., while wearable ones detect target analytes in sweat, tears, saliva, urine, and exhaled gas on the human body surface.

As mentioned above, the efficient management of diseases relies on more accurate and continuous information acquisition from patients. The utilization of flexible biochemical sensors to monitor biochemical indexes can provide abundant information for disease POC management, which is of great significance for disease diagnosis, treatment, intervention, and prognosis. Therefore, in this paper, recent flexible biochemical sensors for management of various diseases, focusing on chronic and communicable diseases, were reviewed, and the detection principle and performance of these flexible biochemical sensors were discussed. Finally, some directions were proposed for further development of flexible biochemical sensors, so as to address the problem of uneven distribution of medical resources and reduce the pressure on central hospitals.

Flexible biochemical sensors for management of three main chronic diseases

Flexible biochemical sensors for cancers

Globally, cancer is the second leading cause of death and is responsible for an estimated 10 million deaths in 2020 (about 1 in 6 deaths is due to cancer) [21]. Therefore, techniques for early diagnosis of cancer have attracted great attention in the past decades. Cancer biomarkers cover a broad range of biochemical entities, such as proteins, nucleic acids, and small metabolites, as well as entire tumor cells and their specific products found in the body fluid or focused tissues, which can be utilized for risk assessment, diagnosis, prognosis, and prediction of treatment efficacy, toxicity, and recurrence [22].

Carcinoembryonic antigen (CEA) is one of the most classic and widely used broad-spectrum tumor biomarkers, which is relevant to tumorigenesis of many cancers including colorectal cancer, lung cancer, liver cancer, breast cancer, etc. Early in 2015, Kumar et al. [23] fabricated a conducting paper–based biosensor comprising of poly (3,4-ethylenedioxythiophene):poly (styrenesulfonate) (PEDOT:PSS) and reduced graphene oxide (rGO) composite for CEA detection, and the results indicated that the conducting paper electrode was a promising alternative over the expensive conventional electrodes for POC devices. Next in 2019, they used nanostructured iron oxide (nFe_2O_3) instead of rGO to form a nanocomposite with PEDOT:PSS [24]. After pretreatment with dimethyl sulfoxide (DMSO), the electrical conductivity of the paper electrode was enhanced by two orders of magnitude, so that the sensitivity, detection range, and shelf life of the biosensor for CEA were further enhanced. In a recent work, Zhu et al. [25] used flexible label-free plasmonic metasurface sensors with gold nanobump arrays for CEA detection (Fig. 1A), which enabled facile surface biofunctionality, high sensitivity, low cost, and simple optical measurement in the visible range. The assay sufficiently covered the threshold concentration of CEA in human serum samples (20 ng/mL) for early cancer prediction.

Prostate specific antigen (PSA) is a well-established tumor biomarker of prostatic cancer. Based on a 3D hierarchical biocomposite comprised of hollow and natural pollen microcapsules coated with a conductive graphene layer, Wang et al. [26] developed an ultrasensitive and flexible biosensor for PSA and obtained an ultrahigh sensitivity detection down to 1.7 fM (Fig. 1B). Compared to conventional 2D graphene-coated sensors, the 3D wearable biosensor showed its real-time feedback and superior performance, which was consistently high across

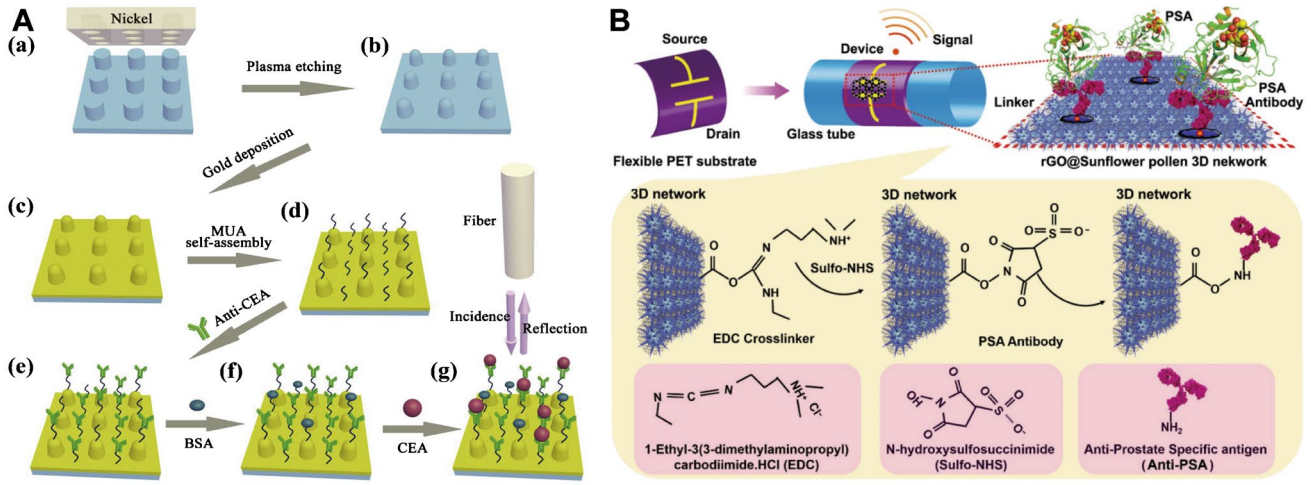

Fig. 1 Flexible biochemical sensors for cancers. **A** Low-cost flexible plasmonic nanobump metasurfaces for label-free CEA sensing, (a)~(c) fabrication process of the plasmonic metasurface, (d)~(g) schematic drawing of bio-functionalization and CEA detection. Reprinted (adapted) with permission from ref [25]. Copyright 2020 Elsevier. **B** Design scheme of a flexible biosensor with graphene-functionalized pollen microcapsules as the sensing element for PSA detection. Reprinted (adapted) with permission from ref [26]. Copyright 2016 John Wiley and Sons

various bending conditions. Yoo et al. [27] developed a flexible epidermal skin–type MoS_2 field-effect transistor (FET)–based biosensors for PSA for POC diagnostics of prostate cancer. PSA at the concentration of 1 pg/mL can be detected, which was several orders of magnitude below the clinical cut-off level of 4 ng/mL.

High level of CA 19–9 is often regarded as a sign of pancreatic cancer. Ibanez-Redin et al. [28] proposed a mechanically flexible electrochemical immunosensor to determine CA 19–9 from serum samples and whole cell lysates, which was based on screen-printed carbon electrodes (SPCEs) coated with layer-by-layer (LbL) films of carbon black (CB) and polyelectrolytes. The antigen–antibody interaction was monitored using differential pulse voltammetry (DPV) and obtained an excellent analytical performance with low LOD of 0.07 U/mL.

In addition to proteins, the significance of microRNA (miRNA) in numerous cancers as key regulators and biomarkers has been recognized and revealed in the last several years [29]. In the study of Na et al. [30], a localized surface plasmon resonance (LSPR)–based miRNA-sensing platform on a flexible and scalable plasmonic nanostructure was developed, which was capable of detecting miR-200a-3p specifically in total RNA extracts from primary cancer cell lines without purification or labeling. The results indicated that the flexible platform might be used in POC cancer diagnostics without the need for gene amplification. Besides, Gu et al. [31] developed a photoluminescent membrane via single-stranded DNA probes attached to flexible and graphene oxide (GO)–coated polyurethane fibers for miRNA-21 detection. Complementary co-hybridization between target miRNA and the corresponding DNA probe led to the release of the upconversion mesoporous silica nanoparticles (MSNs) from the membrane, and therefore, the miRNA quantification was achieved by the upconversion luminescence intensity of the membrane, with LOD of 20 pM.

Hydrogen peroxide (H_2O_2) is involved in various signal transduction pathways and cell fate decisions, so cancer cells can also be characterized by an increased H_2O_2 production rate and its intracellular concentration and localization in comparison to normal cells [32]. For example, Zhang et al. [33] constructed a flexible nanohybrid microelectrode based on carbon fiber wrapped by gold nanoparticle (GNP)–decorated nitrogen-doped carbon nanotube arrays (NCNTAs), which was used for in situ real-time detection of H_2O_2 secreted from live cancer cells. The dense and uniform GNPs exhibited extraordinary electrocatalytic activity to the reduction reaction of H_2O_2, thus helping the microelectrode achieve satisfactory sensing performance including wide linear range, low LOD, and high sensitivity. Moreover, Lyu et al. [34] realized real-time and in situ monitoring of H_2O_2 release from living cells by a stretchable electrochemical biosensor based on vertically aligned gold nanowires. This platform displayed an excellent sensing performance with a wide linear range from 40 μM to 15 mM. Recently, the work of Wang et al. [35] twisted functionalized multi-walled carbon nanotubes into helical fiber bundles to mimic the hierarchical structure of muscle, which was capable of long-term in vivo monitoring of multiple disease biomarkers, including H_2O_2 in the tumors of mice, as well as calcium ions and glucose in the venous blood of cats.

Table 1 Flexible biochemical sensors for cancers

Targets	Principles	Flexible material	Performance	Reference
CEA for colorectal cancer, lung cancer, liver cancer, breast cancer, etc	Electrochemical immunoassay	PEDOT:PSS / rGO	• High sensitivity of 25.8 μA ng^{-1} mL cm^{-2} • Detection range of 1–10 ng mL^{-1}	[23]
	Electrochemical immunoassay	PEDOT:PSS / nFe_2O_3	• High sensitivity of 10.2 μA ng^{-1} mL cm^{-2} • Detection range of 4–25 $ngmL^{-1}$ • Long term stability	[24]
	Chemiluminescence immunoassay	Polycarbonate substrate	• LOD under 20 ng/mL • High sensitivity of 454.4 nm/RIU	[25]
PSA for prostatic cancer	Electrochemical immunoassay	rGO@SFP / PET	• BLOD of 1.7 fM • Real-time feedback • High flexibility	[26]
	Electrochemical immunoassay	MoS_2 FET	• LOD of 1 pg/mL • Real-time feedback • Highly sensitive • Good mechanical durability	[27]
CA 19–9 for pancreatic cancer	Electrochemical immunoassay	CB@polyelectrolytes / PET	• LOD of 0.07 U/mL • Range of 0.01 to 40 U mL^{-1}	[28]
MiR-let-7a/miR-200a-3p	Localized surface plasmon resonance	Plasmonic nanostructure	• LOD of 13 fM for miR-let-7a in buffer • Detecting miRNA in total RNA extracts from primary cancer cell lines	[30]
MiRNA-21	Complementary co-hybridization/upconversion luminescence	Polyurethane fibers	• LOD of 20 pM • Rapid detection	[31]
H_2O_2	Electrochemistry	Carbon fiber	• LOD of 50 nM • Wide linear range up to 4.3 mM • High sensitivity of 142 μA cm^{-2} mM^{-1}	[33]
	Electrochemistry	v-AuNWs/PDMS	• Real-time and in situ monitoring • Wide linear range, from 40 μM to 15 mM • High sensitivity of 250 mA/cm^2/M	[34]
	Electrochemistry	Helical fiber bundles/PDMS	• Long-term in vivo monitoring • Linear range from 0 to 1.0 mM • Sensitivity of approximately 0.84 μA $μM^{-1}$ • Rapid feedback	[35]

The basic information and performance of the above flexible biochemical sensors for cancers are summarized in Table 1. Moreover, a great deal of efforts have been devoted to the flexible biochemical sensors of other novel tumor-distinguished biomarkers, such as telomerase [36], sialic acid [37], and melanoma [38], which all made some exciting achievements.

Flexible biochemical sensors for diabetes

The prevalence of diabetes mellitus (DM) has been rising more rapidly in the past decades due to the modern lifestyle with unhealthy diet, scarce physical activity, overweight body shape, and excessive consumption of tobacco and alcohol [39]. More importantly, high blood glucose can induce

a variety of DM complications, including blindness, kidney failure, heart attacks, stroke, and lower limb amputation, leading to high mortality and morbidity. Hence, real-time and continuous monitoring of the level of blood glucose and timely treatment of insulin adjustment feedback become the vital approach to the high-efficiency management of DM.

In the past 50 years, glucose catalytic biosensor based on glucose oxidase (GOx) has been developed as one of the bioelectronics with the longest history, the most successful commercialization, and the most active research interest, which brought out the glucose meter, the killer application of POCT device [40, 41]. Oxidase-based biocatalytic layers offered high sensitivity toward the target analyte, yet were subjected to such drawbacks as oxygen fluctuations or deficiency and potential electroactive interferences [42]. To solve these problems, Fang et al. [43] developed a minimally invasive glucose biosensor based the flexibly integrated needle-type microelectrode coated with layer-by-layer deposition of Cu nanoflowers, nafion, GOx, and polyurethane (PU) membranes. PU membrane provided an optimal balance between glucose and oxygen transport to the sensing layer and nafion, while mitigating undesired oxidation of electroactive interfering compounds and improving operational stability of mediated glucose enzyme electrodes in human physiological solutions [44]. Apart from PU membrane, Huang et al. [45] constructed flexible enzymatic electrode through the co-immobilization of the glucose oxidase micro-particles (GOx MPs) and multi-walled carbon nanotubes (CNTs) on the inner surface of a gradient-structured hollow fiber membrane (GHM) (Fig. 2A). GHM controlled the transfer of substances and interferences, balanced between oxygen and glucose, and prevented the leakage of enzymes. In 2018, Zhang et al. [46] successfully developed a flexible self-powered implantable skin-like glucometer for real-time detection of blood glucose level in vivo, which ran

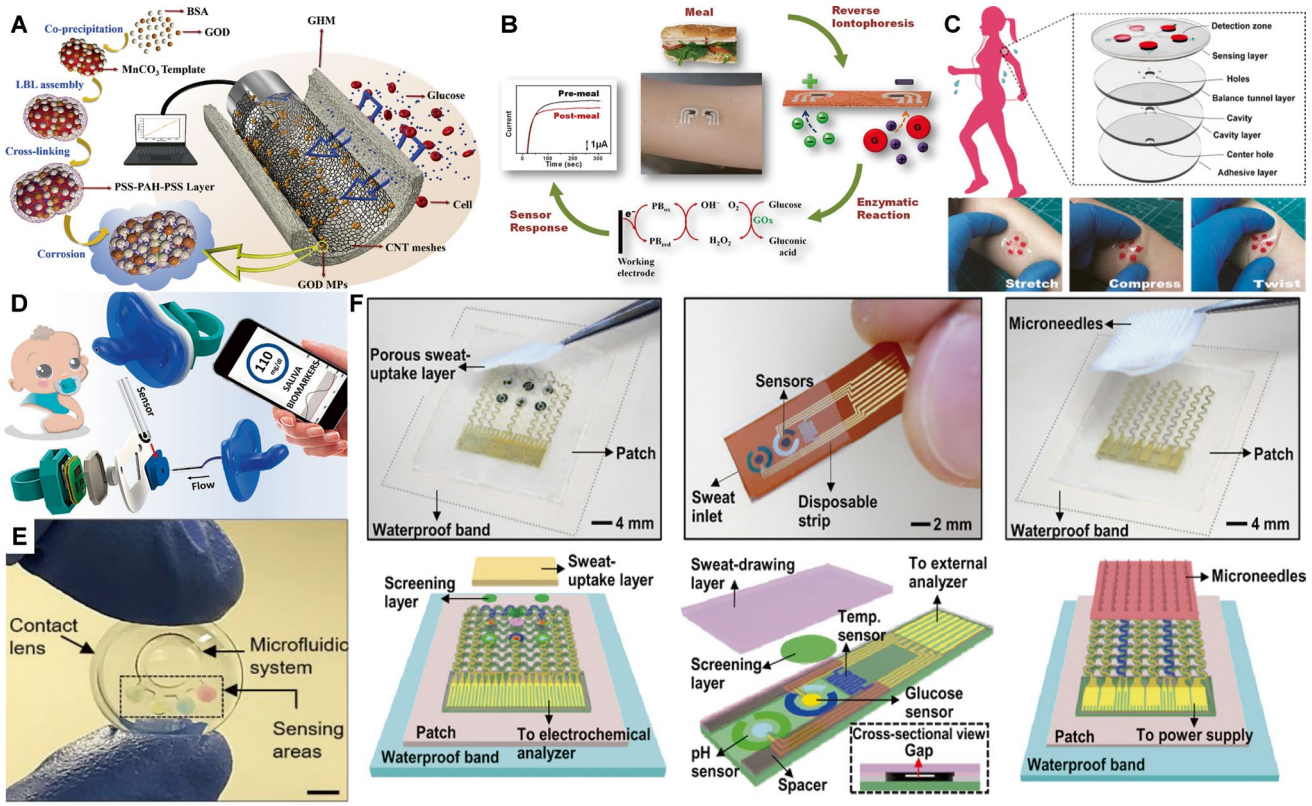

Fig. 2 Flexible biochemical sensors for diabetes. **A** Diagrammatic sketch of the preparation of GOD MPs and the working electrode of the biosensor. Reprinted (adapted) with permission from ref [45]. Copyright 2020 Elsevier. **B** Schematic illustration of tattoo-based noninvasive glucose monitoring. Reprinted (adapted) with permission from ref [51]. Copyright 2014 American Chemical Society. **C** Schematic illustration of the microfluidic chip-based wearable sweat glucose sensor. Reprinted (adapted) with permission from ref [52]. Copyright 2019, American Chemical Society. **D** Pacifier biosensor toward noninvasive saliva biomarker monitoring. Reprinted (adapted) with permission from ref [58]. Copyright 2019 American Chemical Society. **E** Microfluidic contact lenses for the colorimetric sensing of tear metabolites. Reprinted (adapted) with permission from ref [61]. Copyright 2020 Elsevier. **F** Wearable/disposable sweat monitoring device and microneedle-based transdermal drug delivery module. Reprinted (adapted) with permission from ref [66]. Copyright 2017, The Authors

steadily in live mice and realized the glucose level real-time monitoring. The device was based on the piezo-enzymatic reaction coupling effect of GOx@ZnO nanowires and actively output piezoelectric signals containing glucose detection information when deformation was applied.

Although implantable glucose sensing system may assure accurate information and avoid the burden of repeated blood collections, it is quite invasive and requires periodic replacement of the sensor owing to biofouling and the short lifetime [47]. Interstitial fluid (ISF) is regarded as an important body fluid to be used in the management of diabetic patients, where minimally invasive or even noninvasive epidermal glucose sensing was achieved [48–50]. As early as 2015, Bandodkar et al. [51] presented a proof-of-concept demonstration of tattoo-based glucose sensor for noninvasive glycemic monitoring in ISF through reverse iontophoretic extraction of interstitial glucose (Fig. 2B), which indicated the easy-to-wear flexible tattoo-based epidermal diagnostic device possessed considerable promise for efficient diabetes management. Therefore, more focus was paid to noninvasive wearable sensors to estimate glucose levels from sweat [52–55], saliva [56–58], tear [59–62], urine [63], etc.

For sensing the glucose in sweat, Xiao et al. [52] reported a microfluidic chip-based wearable colorimetric sensor using GOx-peroxidase-o-dianisidine reagents (Fig. 2C). Cui et al. [53] for the first time demonstrated a the ratiometric fluorescent nanohybrid-based wearable skin pad, which successfully improved detection sensitivity. In addition, Huang et al. [54] used the reversible binding interaction between pyrene-1-boronic acid (PBA) and glucose to develop an integrated flexible and reusable graphene-based field effect transistor (GFET) nanosensor for monitoring glucose in sweat.

Rising attentions were paid to mouthguard-based biosensor for in vivo salivary glucose measurement recently. In the study of de Castro et al. [56], the feasibility salivary diagnostics on microfluidic paper-based devices (μPADs) was validated and then was further integrated into a mouthguard as a wearable sensor for glucose monitoring. Given that salivary components of ascorbic acid (AA) and uric acid (UA) hindering the accurate measurement of glucose in human saliva, Arakawa et al. [57] developed a wearable mouthguard biosensor coated by cellulose acetate, which can form an interference rejection membrane on a glucose sensor. Besides, Garcia-carmona et al. [58] demonstrated a prototype of an integrated pacifier for non-invasive monitoring of glucose in infant's saliva (Fig. 2D). The infant's oral movement on the pacifier resulted in effective saliva pumping and promoted one-way flow from the mouth to the electrochemical chamber. An integrated electrochemical detection chamber containing enzyme biosensors was located outside the mouth to detect the targets. This baby-friendly pacifier simplified infant health monitoring in a real-time and selective manner, representing the first wearable sensor focused on chemical sensing in newborn saliva.

Emerging efforts were devoted to the detection of glucose in tears. As nitrogen-doped graphene (N-G) is highly electroactive and has flexible property, Zou et al. [59] presented a high-performance intraocular glucose biosensor using carboxylated chitosan-functionalized nitrogen-containing graphene (GC-COOH) immobilized with GOx, which was highly biocompatible to ophthalmologic cells. Moreddu et al. [61] developed microfluidic contact lenses as wearable platforms for in situ tear glucose, pH, protein, and nitrite ions sensing, which provided on-eye screening for monitoring the ocular health both in clinics and at POC settings (Fig. 2E).

Recently, diaper-based monitoring systems have been developed for both physical signals and biomolecular sensing of urine [63, 64]. Li et al. [63] proposed a mechanically flexible diaper-based multiplex electrochemical sensor (MECS) for highly sensitive and selective in situ urine analysis, which simultaneously measured both urinary metabolites (e.g., glucose, H_2O_2, and UA) and electrolytes (e.g., Na^+ and K^+). After being integrated with biosensor modules and communication network, MECS could provide a promising alternative for bedside monitoring of patients with diabetes or other diseases, especially for infants, the disabled and the elderly.

Furthermore, strategies that combine diabetes monitoring and treatment are also worthy of attention. In the study of Lee et al. [65] in 2016, graphene doped with gold was combined with a gold mesh to form a wearable patch for sweat-based diabetes monitoring and feedback therapy. The patch was composed of a heater, temperature, humidity, glucose, and pH sensors and polymeric microneedles that can be thermally activated to deliver drugs transcutaneously. This proposed patch can be thermally actuated to deliver Metformin and reduce blood glucose levels in diabetic mice. In the following year, they further proposed a wearable/disposable sweat-based glucose monitoring device integrated with a feedback transdermal drug delivery module (Fig. 2F) [66]. Drugs for the feedback transdermal therapy were loaded on two different temperature-responsive phase change nanoparticles. This enabled multistage, spatially patterned, and precisely controlled drug release in response to the patient's glucose level, and provided a novel closed-loop solution for the noninvasive sweat-based management of DM.

The basic information and performance of the above flexible biochemical sensors for diabetes are summarized in Table 2. In addition, some studies have recently used flexible biochemical sensors to detect vascular endothelial growth factor (VEGF) [67] and glycated hemoglobin [68, 69], which also showed the promising potential to be utilized as a part of POC management of diabetes. Meanwhile, owing to the advances of nanoscience and nanotechnology, a

Table 2 Flexible biochemical sensors for diabetes

Format	Glucose in	Flexible material	Performance	Reference
Implantable	Blood	PU membranes	• Wide linear range of 0–20 mM • Good sensitivity of 42.38 nA mM^{-1} • Fast response time of less than 15 s	[43]
		Radiant-structured hollow fiber membrane	• High selectivity and reproducibility • Linear sensing range of 0–24 mM • Sensitivity of 25 nA/mM	[45]
		GOx@ZnO nanowires	• Self-powered • Run well in live mouse	[46]
Wearable / noninvasive	ISF	Tattoo base paper	• Detecting micromolar levels of glucose in the presence of common interfering chemical species	[51]
	Sweat	PDMS	• Linear range of 0.1–0.5 mM • LOD of 0.03 mM • Five parallel detections at one time	[52]
		A chitosan film supported by a sticky PU membrane	• Visual monitoring	[53]
		Polyimide substrate	• Range of 0.05–100 mM • LOD of 0.15 μM	[54]
		Silicone	• Integration of monitoring and therapy	[65]
		Polyimide substrate	• Glucose monitoring integrating multistage transdermal drug delivery	[66]
	Saliva	Paper	• Range of 0–2.0 mmol L^{-1} • LOD of 27 μmol L^{-1}	[56]
		MG material/PDMS	• Range of 1.75–10 000 μmol/L	[57]
		PET	• Linear range of 0.1–1.4 mM • LOD of 0.04 Mm • LOQ of 0.1 mM	[58]
	Tear	Corneal contact electrode	• High sensitivity at 9.7 μA mM^{-1} cm^{-2} • Broad linear range at 12 mM • Good detection limit of 9.5 μM	[59]
		Commercial contact lenses	• Responded within a time range of 15 s • Sensitivity of 1.4 nm/mmol L^{-1}	[61]
	Urine	PET	• LOD of 15.5 μM • Sensitivity of 2.71 μA/mM	[63]

*Principles all based on oxidase-based biocatalysis

lot of attention has been paid to novel nanomaterials-based enzyme-free wearable electrochemical and optical sensors for managing and controlling diabetes worldwide [70].

Flexible biochemical sensors for cardiovascular diseases

High prevalence, high disability rate, and high mortality of cardiovascular diseases (CVDs) bring about a major burden in healthcare worldwide and exert a significant economic toll, especially in low- and middle-income countries. Therefore, the flexible biochemical sensors that are able to achieve high-efficiency triage at the first time of onset, or even early warning before symptoms appear via multiplexed real-time dynamic monitoring of related biomarkers, are of great significance for successful management of CVDs, especially under medical resource-limited settings [71–73].

The cardiac troponin I (cTnI) and T (cTnT) are recognized as sensitive and specific biomarkers for myocardial infarction, which are highly recommended in recent guidelines for diagnosis, risk stratification, treatment decisions, efficacy assessment, process monitoring, and prognosis of acute coronary syndrome(ACS) [74–76]; thus, POC monitoring of the two biomarkers has significant benefits on patient care. Shanmugam and Prasad et al. [77, 78] focused on the development of disposable electrochemical flexible immunosensors for cardiac troponin detection based on zinc oxide (ZnO) nanostructure. As early as 2016, they firstly designed and fabricated nanostructured ZnO sensing electrodes on porous polyimide substrates to achieve ultrasensitive and low-volume POC detection of cTnT on flexible strips (Fig. 3B) [77]. And then they established a flexible disposable electrochemical biosensor for rapid and simultaneous detection of cTnI and cTnT (Fig. 3A) [78],

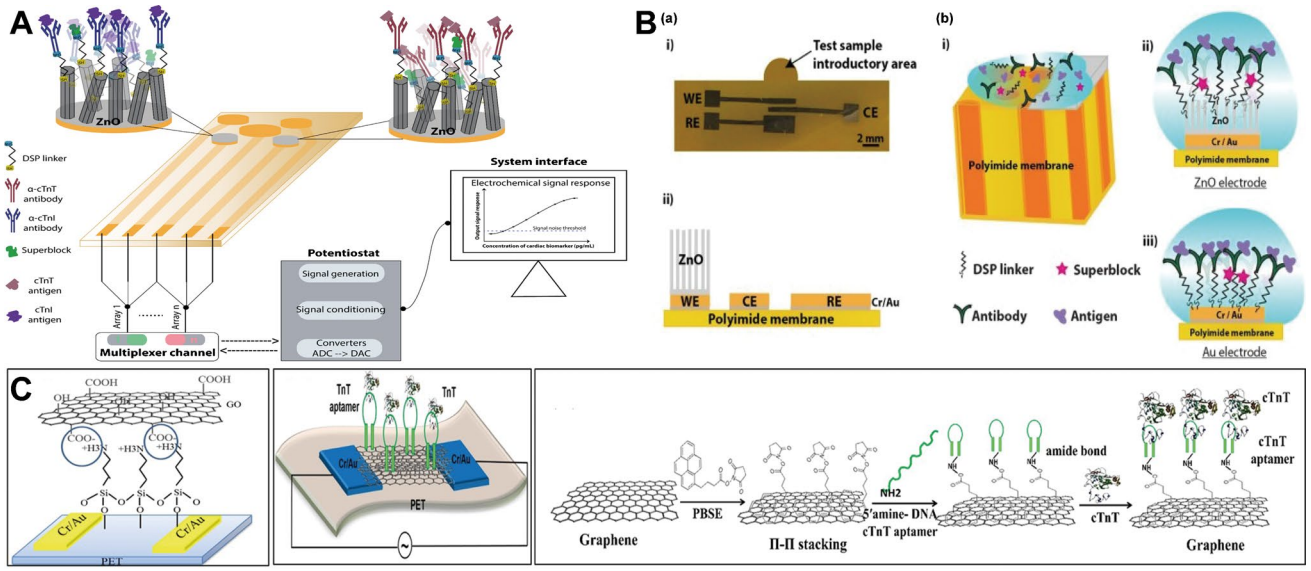

Fig. 3 Flexible biochemical sensors for cardiovascular diseases. **A** Schematic representation of sensing of cTnI and cTnT biomarkers in multiplexed sensor array format. Reprinted (adapted) with permission from ref [78]. Copyright 2016 Elsevier. **B** (a) Schematic representation of disposable flexible strip based electrochemical biosensor platform (i) optical image and (ii) electrode material stack, (b) schematic illustration of (i) sample absorption onto the sensing electrode and immunoassay formed at the electrode/electrolyte interface in (ii) ZnO electrodes and (iii) Au electrodes [77]. **C** Flexible electrical aptasensor using dielectrophoretic assembly of graphene oxide and its subsequent reduction for cardiac biomarker detection [80]

which possessed satisfactory multiplexing and simultaneous detecting performance. The flexible sensor platform was comprised of arrays of high density ZnO nanostructure electrodes functionalized by Troponin, where target cTnI and cTnT were confined. Demirbakan et al. [79] developed a disposable immunosensor using graphite paper (GP) electrodes, and were successfully used to detect cTnT in human serum. Sharma and Jang [80] presented a label-free, low-cost, transparent, and flexible aptamer-based electrochemical biosensor for cTnT detection using rGO sheets (Fig. 3C). Amine-modified single-strand DNA aptamers against cTnT were immobilized onto the rGO channels, which were firstly deposited using dielectrophoresis (DEP) onto a PET substrate with controlled alignment. Moreover, Dong et al. [81] developed a photoelectrochemical immunosensor to determine cTnI in serum based on the flexible indium tin oxide-polyethylene terephthalate (ITO-PET) electrode, where the nanocomposite of Bi_2Se_3 and flower-like $ZnIn_2S_4$ nanospheres (ZIS), as signal amplification material, was modified.

Table 3 Flexible biochemical sensors for cardiovascular diseases

Targets	Principles	Flexible material	Performance	Reference
cTnT	Electrochemical immunoassay	Porous polyimide substrate	• LOD of 1 pg/mL • Good mechanical integrity	[77]
cTnI / cTnT	Electrochemical immunoassay	Polyimide substrate	• LOD of 1 pg/mL in complex media • Good selectivity • Multiplexing and simultaneous detection	[78]
cTnT	Electrochemical immunoassay	Conductive graphite paper	• Wide detection range of 0.5–1000 fg/mL • LOD of 1.28 fg/mL • LOQ of 4.29 fg/mL • Good sensitivity, reproducibility, repeatability, reusability, and long storage life	[79]
cTnT	Aptamer-based electrochemical	PET	• LOD of 1.7 pg/mL in diluted human serum	[80]
cTnI	Photoelectrochemical immunoassay	ITO-PET	• Linear range of 0.08–40 ng/mL • LOD of 0.026 ng/mL • Excellent selectivity, high sensitivity, and good stability	[81]

The electrochemical biosensors mentioned above have ultra-sensitive and dynamic analytical performance for cTn detection with cost-effective flexible materials suitable for large-scale manufacturing and are summarized in Table 3. However, studies on flexible biosensors for other cardiac or thrombus biomarkers (e.g., heart-type fatty acid binding protein (h-FABP), amino-terminal pro-B-type natriuretic peptide (NT-proBNP), and d-dimer) are still relatively rare.

Flexible biochemical sensors for management of other chronic diseases

Flexible biochemical sensors for neurological diseases

A wide variety of neurological diseases can affect the brain and nervous system. Especially, neuropathy can cause neurodegenerative disease (ND), such as Alzheimer's disease (AD) or Parkinson's disease (PD), which have been bothering human beings for a long time.

Among all biochemical molecules, neurotransmitters such as glutamate and acetylcholine play a vital role in the structure and function of the human nervous system. For example, high excitability of glutamate can produce neurotoxicity, which can lead to brain and spinal cord damage. Amyotrophic lateral sclerosis (ALS), AD, PD, traumatic brain, and spinal cord injuries (SCI) are all associated with glutamate excitatory toxicity [82, 83]. Nguyen et al. [84] proposed an amperometric biosensor using ink writing technology for the purpose of in vivo glutamate monitoring (Fig. 4A), which can be inserted into the spinal cord to measure extracellular dynamics of glutamate and other potential biomarkers during a traumatic SCI event with good flexibility, stability, sensitivity, and selectivity. In order to minimize mechanical mismatch between soft neural tissues and implants, and hence improve long-term performance, Wen et al. [85] utilized solid-to-liquid phase changes of gallium (Ga) at body temperature to solve the difficulty of

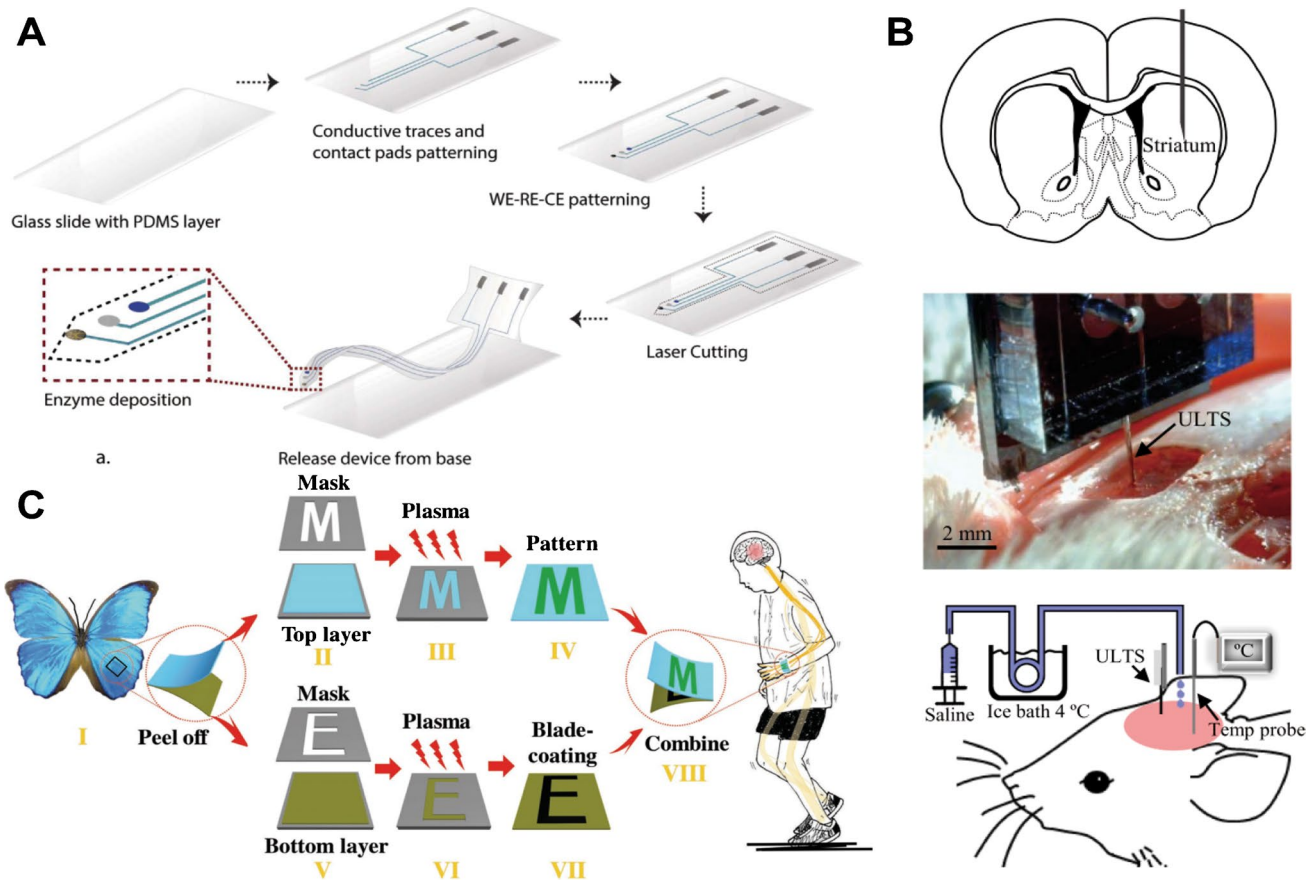

Fig. 4 Flexible biochemical sensors for neurological diseases. **A** Schematic of fabrication process of PtNPs-nanocomposite-based glutamate biosensor on a PDMS substrate. Reprinted (adapted) with permission from ref [84]. Copyright 2019 Elsevier. **B** Flexible, multifunctional neural probe for deep-brain chemical sensing and agent delivery implantation in rats. Reprinted (adapted) with permission from ref [85]. Copyright 2019 Elsevier. **C** Schematic diagram illustrating the fabrication of *M. menelaus*–based wearable sensors. Reprinted (adapted) with permission from ref [86]. Copyright 2018 John Wiley and Sons

flexible probe insertion into deep brain (Fig. 4B). Ga helped insert probes into the brain under cooling conditions and were melt at body temperature to become soft, flexible, and stretchable in all directions. Multilayer deformable microfluidic channels were assembled on the probes for chemical reagent delivery and glutamate sensing.

Natural ordered structures in nature have great potential for the development of ultrasensitive biosensors. He et al. [86] made use of the structural characteristics of wings of *Morpho menelaus* (*M. menelaus*) to develop a disposable flexible biosensor integrated with microfluidic system, immunoassay, and electronic networks for biochemical-physiological hybrid monitoring of ND (Fig. 4C). They separated the bright blue up layer of *M. menelaus* hind wing from the brown under layer. The modified upper layer with a fluorescent enhancement property was used for microfluidic detection of Ad7C-NTP (AD-associated neuronal thread protein) using immunoassays, and the conductive ink-coated lower layer was used for electronic sensing of the static tremor frequency of patients. The *M. menelaus*–based biosensor was then attached to a finger or a wrist for movement monitoring and biomarker detection.

Table 4 Flexible biochemical sensors for other chronic diseases

Diseases	Targets	Principles	Flexible material	Performance	Reference
Neurological diseases	Glutamate for ALS, AD, PD, SCI, traumatic brain, etc	Amperometric biosensing	Flexible polymer substrate	• Good selectivity, repeatability, and stability • Biased at 0.5 V, linear range of 1 μM—800 μM, LOD of 0.5 μM, response time < 3 s • Biased at − 0.2 V, linear range of 10 μM—600 μM, LOD of 0.2 μM, response time ~ 15 s	[84]
		Electrochemical sensing	PDMS	• Sensitivity of 8.2 ± 1.2 pA/μM • LOD of 0.39 ± 0.07 μM • Response time of ~ 1 s	[85]
	AD7c-NTP for AD and PD	Immunoassay	M. menelaus' wing	• Range of 10 to 500 ng mL^{-1} • LOD of 4.5 ng mL^{-1}	[86]
Chronic respiratory diseases	H_2O_2 for asthma, COPD, lung cancer, etc	Amperometric differential electrochemical measurement	Chromatography paper	• Range of 40–320 μM • Sensitivity of 0.02 nA μM^{-1} mm^{-2}	[89]
	Chlorine for CF	Electrochemical sensing	A flexible nanoporous substrate	• Good sensitivity • Wide linear range of 10–100 mM	[91]
Inflammation	TNF-α	Electrochemical immunoassay	3D micro-patterned elastomeric substrate	• Ranging from 100 fM to 100 nM • LOD of 100 fM in the PBS • LOD of 1 pM in the serum • High stability and durability	[104]
	IFN-γ	Aptameric GNFET	Graphene-Nafion composite film	• Detection range from 0.015 to 250 nM • LOD of 740 fM • Durability and flexibility	[105]
	Glucose	Electrochemical sensing	Polyimide substrate	• Sensitivity of 7.17 μA/mM cm^2 • LOD of 10 μM, • Significant selectivity	[106]

The basic information and performance of the above flexible biochemical sensors for neurological diseases are summarized in Table 4. It can be seen that there are not many studies on flexible biochemical sensors for neurological diseases, which might be caused by the complexity and fragility of the nervous system. Detection or intervention of the nervous system requires particularly delicate, precise design, and operation. The materials used in implantable flexible sensors must have high biocompatibility, while non-implantable ones may not achieve ideal accuracy due to various interference factors. Thus, more advances are needed in flexible biochemical sensors for monitoring neurological diseases.

Flexible biochemical sensors for chronic respiratory diseases

Chronic respiratory diseases, for example, asthma, bronchiectasis, lung cancer, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), sleep apnea (SA), occupational lung disease (OLD), and pulmonary hypertension (PH), affect people of all ages and have an unignorable impact not only on the individual, but also on the family, the community, and the healthcare system [87]. Respiration is a continuous process, so the development of flexible biosensors for simultaneous and continuous monitoring of multiple related biomarkers or other biomolecules is of great significance for the nursing of patients with chronic respiratory diseases.

H_2O_2 which also can be detected in exhaled gas is an important biomarker associated with asthma, COPD, and lung cancer [88]. However, conventional respiratory analysis methods are often not conducive to continuous or real-time gas condensation, complicating patient monitoring on a regular or long-term basis. A low-cost, disposable, and no calibration required paper-based electrochemical wearable sensor was proposed to solve this problem, which can be integrated into a commercial breathing mask for continuous and real-time detection of H_2O_2 in exhaled gas [89] (Fig. 5A). In this sensor, Maier et al. used an amperometric differential electrochemical measurement with silkscreen printed Prussian blue mediated and non-mediated carbon electrodes to effectively improve the detection accuracy. The system can be extended to continuously monitor other analytes in exhaled gas versatilely by changing the chemical properties of the sensing electrode.

Chlorine content in sweat is important for the diagnosis and prognosis of CF [90]. The current methods for active stimulation of sweat glands, such as treadmill runs and iontophoresis, are not suitable for the geriatric, pediatric, and other population with low immune function or physical inactivity. Therefore, Ganguly et al. [91] demonstrated a novel flexible electrochemical biosensor for passive and ultra-low sweat chloride assessment in ultra-low volumes (1–3 µL) of human sweat eluted at natural rates (Fig. 5B). The obtained results showed that the developed biosensor had a higher sensitivity than that of the currently available sweat chloride sensing schemes.

The basic information and performance of the above flexible biochemical sensors for chronic respiratory diseases re summarized in Table 4. Remarkably, exhaled NOx (including NO and NO_2) is widely regarded as a biomarker for respiratory diseases [88, 92, 93]. Many studies have conducted

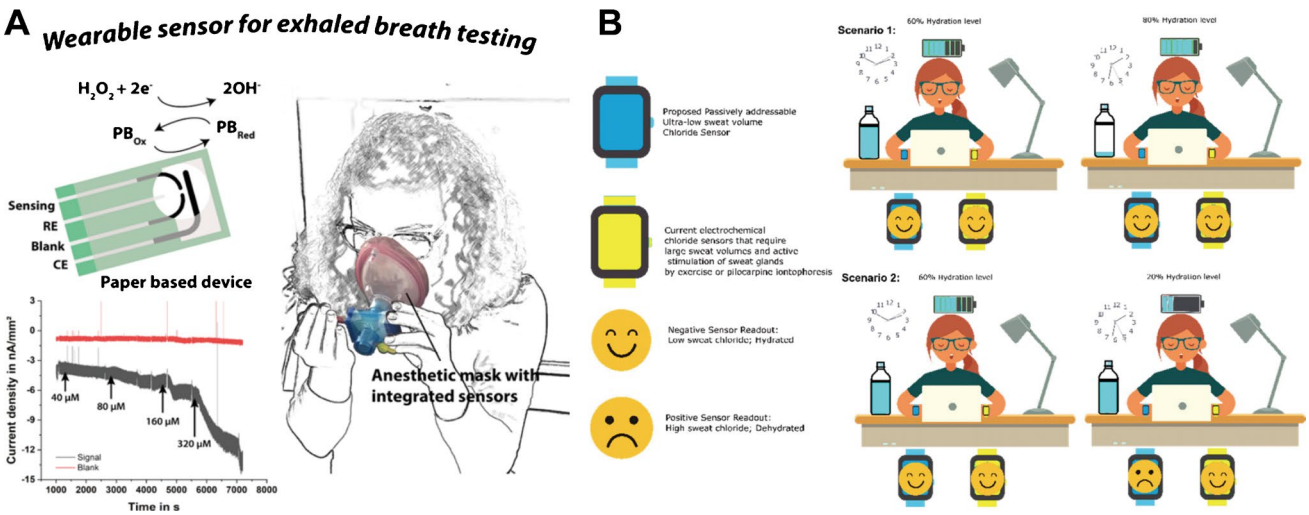

Fig. 5 Flexible biochemical sensors for chronic respiratory diseases. **A** A paper-based wearable sensor for real-time hydrogen peroxide measurement in simulated breath. Reprinted (adapted) with permission from ref [89]. Copyright 2019 American Chemical Society. **B** Passively addressable ultra-low volume sweat chloride sensor. Reprinted (adapted) with permission from ref [91]. Copyright 2019 MDPI

for sensitive NOx sensors development based on novel materials, such as MXenes [93], WO_3 [94–96], Cu_xO/graphene [97], SWCNT [98], ZnO/p-Si nanowire (NW) [99], and Zn1-xNixO [100], which were expected to be further used as related flexible or wearable biochemical sensors.

Flexible biochemical sensors for inflammation

It is worth noting that chronic inflammation is a vital factor to serious chronic diseases mentioned above [101]. When the innate immune system (IIS) activity is incorrect or excessive in human body, the chronic inflammation can be activated, which will enhance the prevalence of chronic diseases [101–103]. Thus, monitoring of inflammation with flexible biosensors may be able to discover clues in time to reduce the incidence rate of chronic diseases.

Kim et al. [104] developed a stretchable electrochemical immunosensor based on stable and durable metal electrodes with 3D geometric engineering for tumor necrosis factor-α (TNF-α) cytokine detection in human serum (Fig. 6A). The device had high stability and durability due to the use of a unique 3D micro-patterned elastomeric substrate. It was expected to be integrated into the body-attachable immune sensing platform, providing a new method for detecting small biomolecules or proteins in various body fluids. In a later study, a regenerative and flexible aptameric graphene-Nafion field-effect transistor (GNFET) biosensor was developed (Fig. 6B) [105]. The graphene-Nafion composite film effectively eliminated the interferences of nonspecific adsorption and enhanced the regeneration ability of GNFET. In addition, due to the durability and flexibility of graphene-Nafion composite film, the device can withstand cyclic crumpling tests and was conformed to body surface. The biosensor was sensitive to IFN-γ in undiluted human sweat under different conditions, and the limit of detection (LOD) was 740 fM. Sharp local fluctuations in glucose concentration can be considered to trigger pro-inflammatory activation, and Lee et al. [106] designed an enzymeless glucose sensor integrated with a chronically implantable nerve cuff electrode for continuous and stable in-situ monitoring of local inflammation (Fig. 6C). It was believed that understanding glucose metabolism through local implantable devices was likely to contribute to the internal adjustment and treatment of pro-inflammatory or chronic inflammation.

Therefore, monitoring chronic inflammation with flexible biochemical sensors is conducive to in-depth exploration of pathology and early intervention, which may improve the efficacy of treatments, thereby transforming the chronic pro-disease environment into an anti- disease environment [107]. The basic information and performance of the above flexible biochemical sensors for inflammation were summarized in Table 4.

Flexible biochemical sensors for management of communicable diseases

A great number of communicable diseases, for example, viruses (e.g., HIV, dengue virus and Ebola virus) and bacteria (e.g., *Yersinia pestis* and *Vibrio cholerae*), have been posing a serious threat to human health. To date, the COVID-19 caused by SARS-CoV-2 still remains serious. The spread of communicable diseases is usually relatively wide, so the medical observation, detection, and screening are laborious and time-consuming. Thus, the real-time monitoring of related vital signs and disease biomarkers is highly demanded.

Nucleic acid detection is an important way for screening patients with communicable diseases. In the primary medical care with limited resources, the combination of isothermal amplification and biochemical sensors can meet various needs of pathogen detection. Yang et al. [108] developed a novel bandage-like wearable and flexible microfluidic sensor based on recombinase polymerase amplification (RPA) for rapid and visual detection of a conservative fragment of Zika virus (Fig. 7A). The wearable sensor was triggered by human body temperature (30–37 ℃), and the results were obtained within 10 min with good sensitivity, accuracy, and selectivity. Kong et al. [109] developed a wearable microfluidic device combined with RPA to realize simple and rapid HIV-1 DNA amplification using heat from human wrists (Fig. 7B). With the help of a smartphone-based fluorescence detection system, the device was able to quantitatively detect HIV-1 DNA within 24 min. When wearing a mask, the virus can accumulate inside the mask as a result of coughing, talking, or breathing [110, 111]. Nguyen et al. [112] demonstrated a mask with a clustered regularly interspaced short palindromic repeats (CRISPR) based sensor for noninvasive detection of SARS-CoV-2 at room temperature within 90 min, which only needed the press of a button.

Another way to identify communicable diseases is to detect proteins associated with the virus with the presence of antibodies immobilized on some nanomaterial. MoS_2, as a transition metal dichalcogenide (TMD), has been widely used in biosensors due to its electric charge effect, semiconducting/electrochemical property, and biocompatibility [113–117]. Shin et al. [118] developed an electrochemical flexible biosensor consisting of MoS_2 nanoparticles, gold (Au), and Au (Au/MoS2/Au nanolayers) on a PET substrate for the detection of GP120, the HIV-1 surface protein (Fig. 7C). Zhang et al. [119] effectively stripped high-quality natural MoS_2 crystal based on electrochemical strategy, and the obtained MoS_2 dense film was successfully biofunctionalized with anti-Ebola VP40 antibodies to make flexible biosensor with excellent

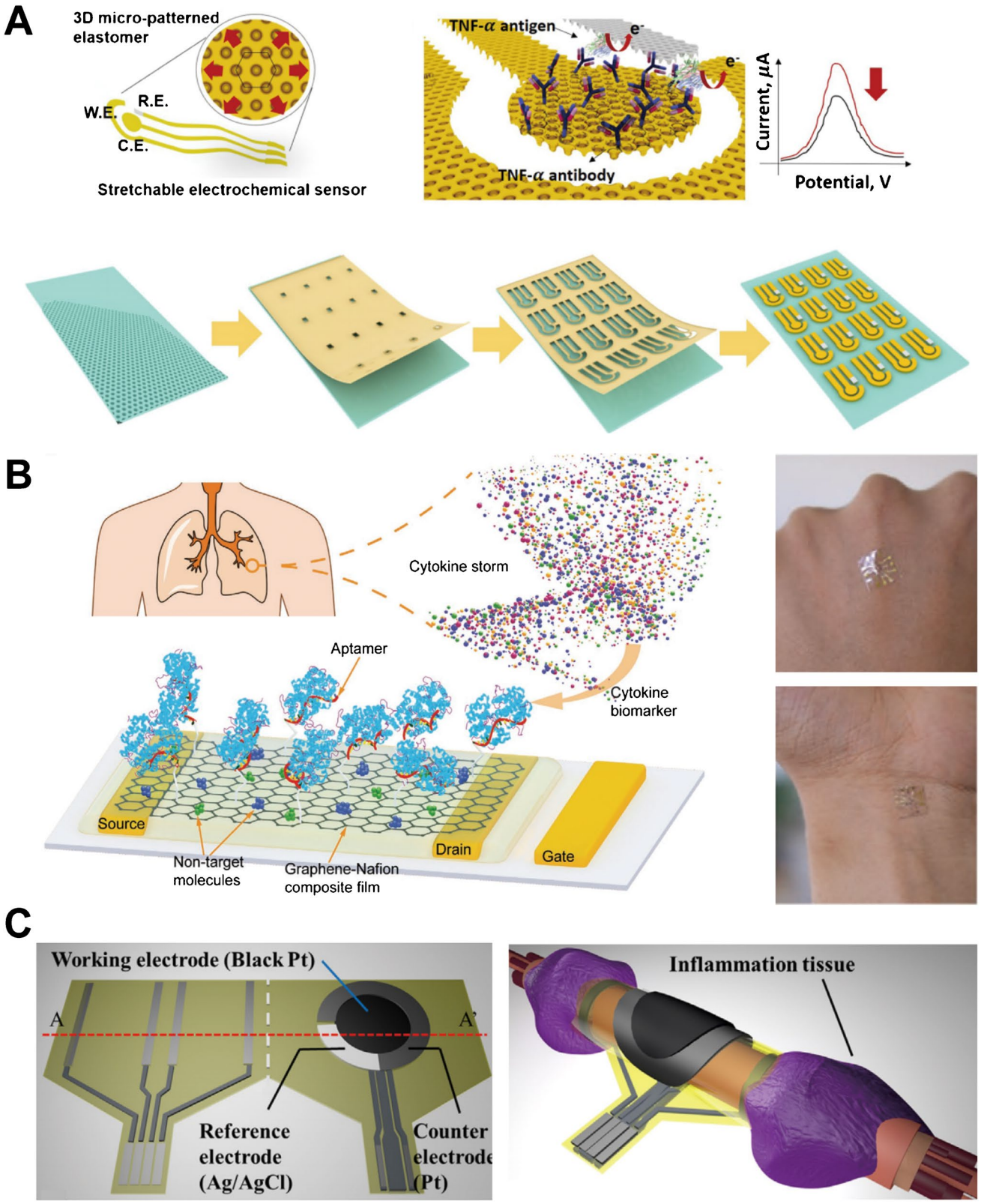

Fig. 6 Flexible biochemical sensors for inflammation. **A** Scheme of a stretchable electrochemical immunosensor fabricated on 3D micro-patterned elastomeric substrate. Reprinted (adapted) with permission from ref [104]. Copyright 2018 Elsevier. **B** Graphene-Nafion field-effect transistor (GNFET) biosensor for cytokine biomarker detection. Reprinted (adapted) with permission from ref [105]. Copyright 2020 John Wiley and Sons. **C** Enzymeless glucose sensor integrated with chronically implantable nerve cuff electrode for in-situ inflammation monitoring. Reprinted (adapted) with permission from ref [106]. Copyright 2015 Elsevier

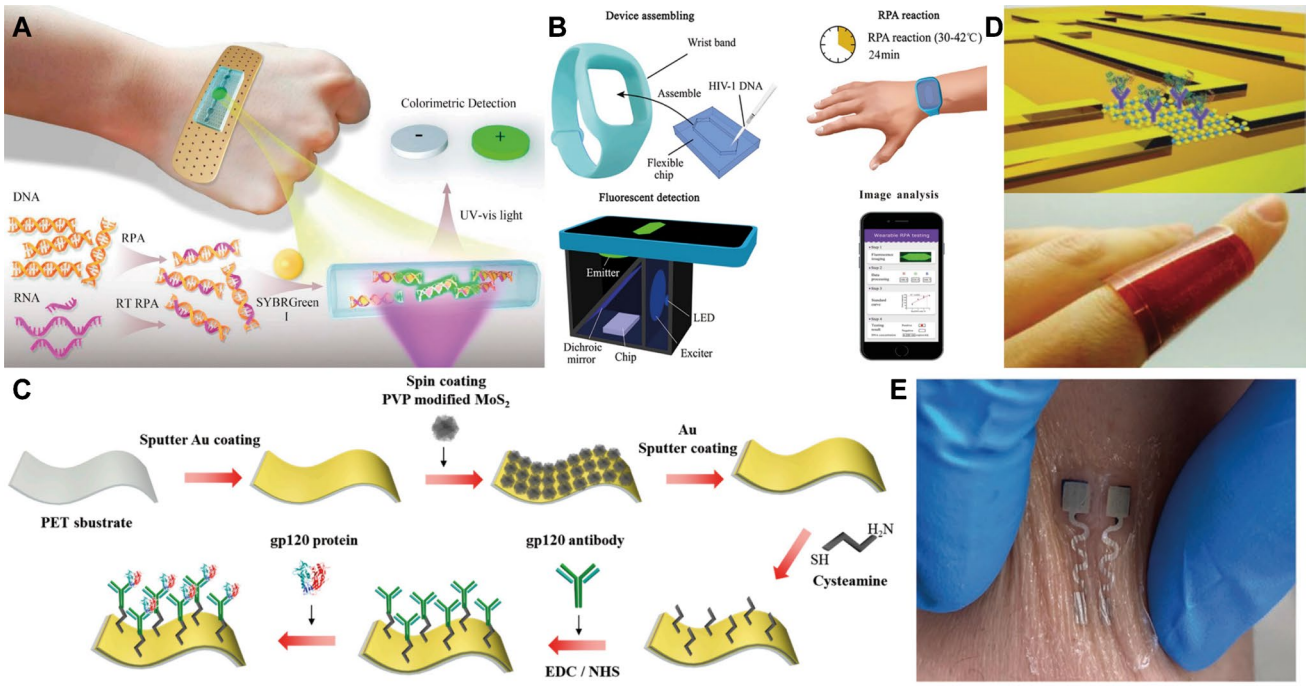

Fig. 7 Flexible biochemical sensors for communicable diseases. **A** Bandage-like wearable flexible microfluidic recombinase polymerase amplification sensor for the rapid visual detection of nucleic acids. Reprinted (adapted) with permission from ref [108]. Copyright 2019 Elsevier. **B** Schematic of wearable RPA testing for rapid detection of HIV-1 DNA. Reprinted (adapted) with permission from ref [109]. Copyright 2019 Elsevier. **C** Flexible HIV-1 biosensor based on the Au/MoS2 nanoparticles/Au nanolayer on the PET substrate. Reprinted (adapted) with permission from ref [118]. Copyright 2019 MDPI. **D** Multiflake thin-film flexible biosensors for *Ebola* VP40 detection. Reprinted (adapted) with permission from ref [119]. Copyright 2019 John Wiley and Sons. **E** Na^+ MN-EGFET biosensor patch showing high skin conformability. Reprinted (adapted) with permission from ref [124]. Copyright 2022 John Wiley and Sons

analytical performance for Ebola (Fig. 7D). Early in 2016, GFET were built on flexible substrates as a biosensor to detect communicable organisms by immobilizing antibodies on graphene [120, 121]. After the COVID-19 outbreak, Cui et al. [122] proposed a laser-induced graphene field-effect transistor (LIG-FET) on a flexible PI

Table 5 Flexible biochemical sensors for communicable diseases

Disease	Targets	Principles	Flexible material	Performance	Reference
Zika	Zika virus	RPA / colorimetric detection	Ecoflex material / PDMS	• Detection limit of 10 copies/μL • Highly sensitivity and selectivity • Detection within 10 min	[108]
AIDS	HIV-1 DNA	RPA / fluorescence detection	PDMS	• Ranging from 102 to 105 copies/mL • LOD of 100 copies/Ml • Within 24 min	[109]
	GP120	Electrochemical immunoassay	PET	• Ranging from 0.1 pg/mL to 10 ng/mL • LOD of 0.066 pg/mL	[118]
COVID-19	SARS-CoV-2	CRISPR / fluorescence detection	Paper	• LOD of 500 copies (17 aM) • Within 90 min	[112]
		Electrochemical immunoassay	PI film	• LOD of 1 pg/mL • In 15 min	[122]
	Sodium	Electrochemistry	SIS film	• High sensitivity of sensitivity is 5.61 mA mM^{-1} • Low detection limit of 2.78×10^{-6} M • Fast response • Good biocompatibility • Excellent mechanical stability	[124]
Ebola	Ebola VP40	Electrochemical immunoassay	Polyimide substrate	• LOD down to femtomolar levels • Good surface regeneration capability	[119]

film to detect SARS-CoV-2 in 15 min. It is worth noting that dysnatremia is a main prognostic factor of COVID-19 [123], so a flexible microneedle expanded-gate FET biosensor was proposed for real-time monitoring of sodium in ISF with fast response, high sensitivity, low detection limit, good biocompatibility and excellent mechanical stability (Fig. 7E) [124].

The basic information and performance of the above flexible biochemical sensors for communicable diseases are summarized in Table 5. As it turned out, portable and flexible biochemical sensors have the potential to help distinguish susceptible people at home or primary health care institutions, and play an important role in the whole process of treatment and prognosis. It can not only improve the efficiency of detection and screening, but also reduce the burden and cost of central medical treatment. However, the mutation characteristics of viruses and bacteria have high requirements for the renewal of biochemical sensors, which is a huge challenge.

Conclusions and perspectives

The advances of flexible biochemical sensors for various diseases management were contributed to the improvement of POC healthcare. Based on novel flexible materials, in the form of implants or wearables, by detecting disease-related biomarkers in human physiological fluids, flexible biochemical sensors showed great real-time monitoring potential in the early screening, diagnosis, treatment, and prognosis of chronic and communicable diseases, so as to reduce the burden of central hospitals and alleviate the shortage of medical resources. However, the development of flexible biochemical sensors still faces many challenges. Herein, some prospective directions were presented as follows.

Firstly, synthesizing novel flexible materials with highly expected properties of higher biocompatibility, stability, malleability, flexibility, biodegradability, and self-healing ability to further promote the function and performance of flexible biochemical sensors.

Secondly, integrating flexible biochemical sensors with implantable soft electronics or wearable physical sensors to develop high-density sensor arrays with multiple functions for simultaneously monitoring of human motion and biochemical indexes.

Thirdly, combining electrochemical energy storage devices based on flexible materials with biofuel cells or novel physical power generation materials to improve the flexibility of the whole sensing system and realize self-power supply for wearable and implantable biochemical sensors.

Finally, integrating flexible biochemical sensors into Internet of things (IOT), artificial intelligence (AI), and machine learning (ML) to shift healthcare from the advanced system to preventive, predictive, participatory, and personalized (4P) medical system to prevent diseases and promote everyone's health lifestyle.

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Declarations

Competing interests The authors declare no competing interests.

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