CRITICAL REVIEW

Minimally and non-invasive glucose monitoring: the road toward commercialization

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The increasing global prevalence of diabetes has led to significant advancements in glucose monitoring technologies. Since the introduction of enzyme-based glucose biosensors in the 1960s, these devices have evolved to enable real-time and dynamic glucose monitoring, with electrochemical biosensors playing a crucial role. Recent innovations have expanded glucose sensing into non-invasive and minimally invasive methods, utilizing optical, millimeter wave, ultrasound, and bioimpedance techniques to provide user-friendly and painless alternatives. This review examines the current state and future prospects of glucose monitoring technologies, particularly focusing on wearable sensors for *in vivo* applications. It explores the key mechanisms of electrochemical and alternative sensing methods, highlighting their evolution, adaptability to different biofluids, and integration into multiplexed systems for improved diabetes management. Emerging wearable devices offer continuous and real-time feedback, which is essential for effective glucose regulation. The review also addresses challenges such as biocompatibility, accuracy in fluctuating physiological conditions, and external factors that can affect sensor performance. Furthermore, it analyzes the commercial landscape, from established continuous glucose monitors to next-generation technologies, highlighting opportunities for personalized care. The aim of this review is to guide future research in developing advanced and efficient glucose monitoring solutions tailored to meet patient needs.
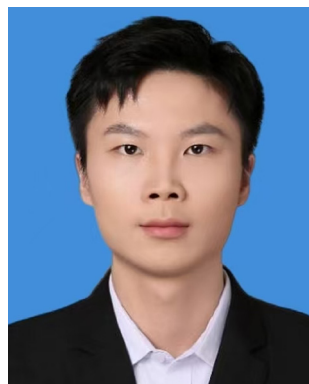
1. Introduction

Diabetes mellitus (DM) has become a significant global health issue. Currently, over 422 million people worldwide are affected by this chronic metabolic disease, which means approximately one in ten adults is affected, and this proportion continues to grow. Diabetes seriously affects human health, and poorly controlled blood sugar levels can lead to various complications such as neuropathy, cardiovascular diseases, renal failure, and retinopathy, causing great suffering to patients and even jeopardizing their lives.[1] Diabetes is caused by insufficient insulin production by the pancreas or inadequate utilization of insulin by the body's cells.[2] DM can be roughly classified into

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type 1 (T1D), type 2 (T2D), and gestational diabetes based on the way and time of onset.[3] Type 1 diabetes is caused by insufficient insulin production, leading to a sudden drop in blood sugar levels, while type 2 diabetes results from inadequate insulin utilization, causing a rise in blood sugar levels.[4] Gestational diabetes is a medical complication occurring during pregnancy.[5] Current clinical methods cannot cure diabetes, and the main ways to alleviate and control it include insulin injections, taking antidiabetic medications, maintaining physical activity, healthy eating, weight management, and regular blood sugar monitoring.[6]

For diabetes, a progressive disease, early diagnosis, effective treatment, and ongoing management are crucial for slowing disease progression and helping patients maintain optimal quality of life.[7] Accurate diagnosis and comprehensive management are essential for effective treatment and the quality of life of diabetes patients. Various invasive and non-invasive technologies used for diagnosing and managing diabetes each have their advantages and disadvantages. While invasive methods like self blood glucose monitoring (SBGM) and continuous glucose monitoring (CGM) provide precise blood sugar measurements, they can cause discomfort and carry the risk of infection and tissue damage.[8] Minimally invasive and non-invasive methods, designed to reduce patient discomfort and enhance compliance, have received significant attention and development in recent years. The importance of efficient blood sugar monitoring technologies extends beyond medical treatment, affecting lifestyle changes, treatment decisions, and overall health.[9] By continuously or periodically testing blood sugar levels, the impact of medications, diet, and exercise on blood sugar levels can be more effectively

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assessed. This enables patients to timely adjust their treatment plans, keep blood sugar within target ranges, reduce or delay the onset of diabetes complications, and improve their quality of life.[10]

The field of minimally invasive and non-invasive blood glucose monitoring technology has garnered significant attention and is continuously evolving. Researchers are dedicated to developing a method for continuous blood glucose level monitoring to achieve minimal or painless experiences, while integrating artificial intelligence technology to provide comprehensive glucose assessment.[11] This review evaluates minimally invasive and non-invasive blood glucose monitoring technologies, detailing their mechanisms, advantages, limitations, and clinical applications. It aims to enhance understanding of both current and emerging technologies, providing insights for researchers, clinicians, and industry stakeholders. By examining the development of glucose monitoring technologies, this review highlights future directions and innovative opportunities, contributing to better diabetes management and improved patient outcomes.

In recent years, there has been a surge in the demand for innovative blood glucose monitoring methods. Scientists and researchers have been actively exploring and developing a range of new non-invasive and minimally invasive blood glucose monitoring technologies, encompassing areas such as sweat,[12,13] tears,[14,15] saliva,[16,17] interstitial fluid,[18,19] blood vessels,[20,21] and physical methods,[22,23] as shown in the Fig. 1. These new technologies not only offer more convenient and comfortable blood glucose monitoring methods but also have numerous potential advantages over traditional finger-prick blood glucose monitoring. In the following section, we will provide a detailed introduction to these new technologies.

2. Glucose monitoring methods

The key to effectively managing diabetes lies in understanding and monitoring blood sugar levels. For a healthy individual, the blood sugar concentration should fall within the range of 70 mg dL^{-1} (3.9 mmol L^{-1}) to 180 mg dL^{-1} (10 mmol L^{-1}).[24] Biomarkers like glycated hemoglobin (HbA1c) and glycated albumin provide valuable insights into blood sugar levels, enabling personalized diabetes management.[25] Tracking the glycemic index of food intake is crucial, as it directly impacts blood sugar levels.[26] Foods with a high glycemic index lead to rapid spikes in blood sugar, while those with a low glycemic index result in slower, steadier increases. Therefore, carefully monitoring calorie intake and carbohydrate consumption is vital for effective diabetes management. Additionally, continuous measurement of key diabetes biomarkers, such as insulin and ketones, is essential for successful diabetes management.[27] It's important to note that insulin, a hormone that regulates glucose uptake into cells, plays a critical role in diabetes management.[28] Keeping insulin levels in check is crucial, as excessive insulin secretion is common in the early stages of type 2 diabetes.[29] By proactively monitoring and adjusting insulin levels, individuals can significantly improve their diabetes management and overall quality of life. Moreover, maintaining a healthy level of physical activity and fitness can positively influence basal
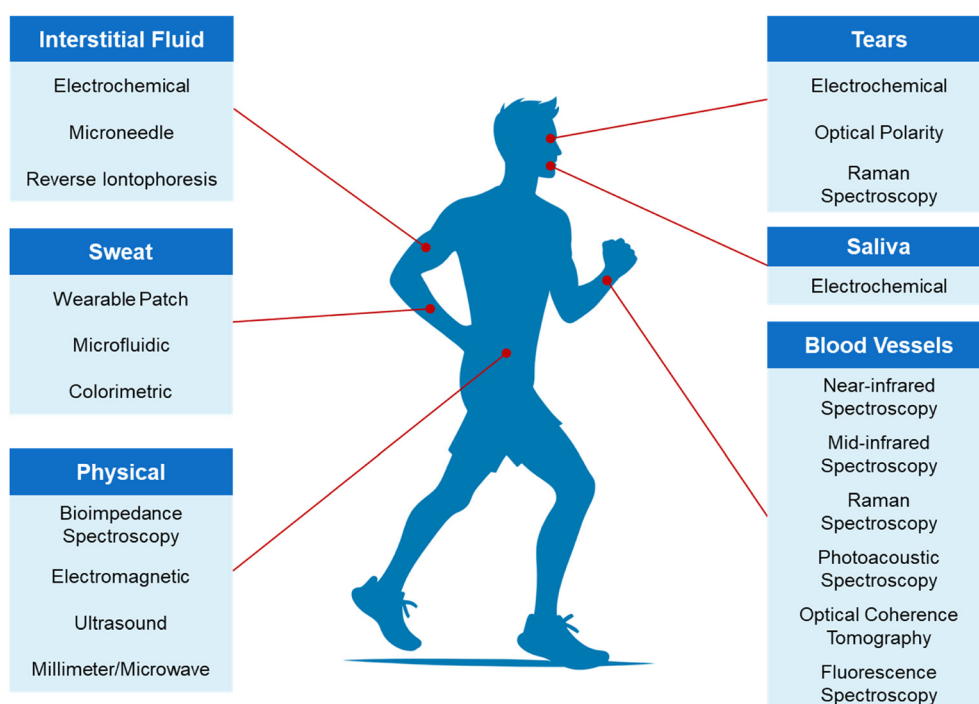

Fig. 1 Classification of minimally and non-invasive glucose sensing techniques.

metabolic rate and glucose metabolism, ultimately contributing to better diabetes management.[30]

2.1. Conventional methods

The self-monitoring of blood glucose (SMBG) is a vital component of diabetes management. It involves collecting a small blood sample from the fingertip and using electrochemical methods to analyze the glucose level, providing immediate information about the user's blood sugar level.[31] Traditional portable blood glucose monitoring devices consist of three main parts: an electrochemical sensor, a measuring instrument, and a display. After obtaining a blood sample, the glucose oxidase in the electrochemical sensor reacts with the blood, producing an electric current signal that is directly proportional to the glucose concentration.[32] This result is displayed on the device's screen for the user's reference and record. Despite its effectiveness, this method has limitations. It requires multiple daily blood collections using needles, causing discomfort and potential infection. Additionally, it does not provide continuous blood glucose monitoring data. Therefore, an ideal blood glucose testing method should offer continuous monitoring and be minimally invasive or non-invasive.

The rapid advancements in sensor and enzyme technology have given rise to the revolutionary continuous glucose monitoring technology. CGM systems represent a cutting-edge approach to glucose monitoring, involving the continuous tracking of a patient's glucose levels through the implantation of a sensor under the skin.[33,34] Comprising a sensor, transmitter, and display device, the CGM system functions by implanting the sensor in subcutaneous tissue to monitor glucose levels in the interstitial fluid. This sensor reacts with glucose molecules, generating a current signal through an electron transfer. The transmitter then transmits the data to an external device, where real-time blood glucose values are calculated using algorithms, enabling users to stay informed about their blood glucose levels at all times.[35] The key advantage of CGM lies in its ability to provide 24 hour continuous monitoring, timely detection of glucose fluctuations and trends, and alerts for high and low blood glucose levels, thereby aiding in the prevention of severe blood glucose fluctuations.[36] Notably, CGM is adept at detecting covert high and low blood glucose levels that traditional testing methods may miss, particularly in monitoring postprandial hyperglycemia and nocturnal asymptomatic hypoglycemia.[37] However, it is important to note that the sensors of the CGM system require regular replacement (approximately every 14 days) and entail high usage costs. Furthermore, CGM systems carry the risk of infection and sensor failure due to long-term wear, as well as potential inaccuracies in blood glucose data caused by physical activity, collisions, and medication interference.

The traditional methods for blood sugar testing, such as the oral glucose tolerance test (OGTT) and the hemoglobin A1c (HbA1c) test, are widely used for diagnosing diabetes and evaluating blood sugar levels.[38,39] While the OGTT provides a comprehensive assessment of glucose tolerance and insulin response, it is time-consuming and may cause discomfort for some patients.[40] On the other hand, the HbA1c test offers a convenient and reliable way to measure long-term blood sugar control but may not capture short-term fluctuations and could be affected by certain health conditions.[41] Each method has its advantages and limitations, and understanding these differences can help individuals and healthcare professionals make informed decisions about managing diabetes and monitoring blood sugar levels effectively.

In conclusion, traditional methods of blood glucose monitoring include self-monitoring, continuous monitoring, oral glucose tolerance testing, and glycated hemoglobin testing. While these methods play a crucial role in the diagnosis and management of diabetes, they still have inherent limitations and drawbacks. Therefore, the development of new blood glucose monitoring technologies is particularly necessary. The development of new technologies should focus on improving the shortcomings of existing technologies and exploring innovative blood glucose monitoring methods, such as non-invasive/minimally invasive monitoring technologies based on optical, acoustic, or biosensors. This will further enhance device comfort and wearability, reduce usage costs, and improve accuracy and stability.

2.2. Electrochemical methods

The development of electrochemical glucose biosensors has evolved through four main stages based on different electron transfer mechanisms, including the classic glucose oxidase (GOx) electrode sensor, the mediator GOx electrode sensor, and the direct GOx electrode sensor, and non-enzyme glucose sensor, as shown in Fig. 2.

The first generation of glucose sensors used glucose oxidase and oxygen as the enzyme's co-factor to measure glucose concentration by detecting the hydrogen peroxide (H_2O_2) produced during the glucose oxidation reaction.[42,43] However, these sensors had limitations as they relied on the availability of oxygen in the environment and were prone to interference from other electroactive substances. To overcome these limitations, researchers made various improvements such as using diffusion-limiting polymer membranes, oxygen-rich carbon pastes, and enzyme modifications.[44] Although these improvements partially addressed the oxygen dependence and interference issues, they still restricted the application of first-generation sensors.

The second generation of enzyme-based biosensors introduced synthetic redox mediators to replace natural oxygen as the electron acceptor, thus overcoming the dependency on oxygen.[45] These redox mediators facilitate rapid and reversible electron transfer between the enzyme's redox center and the electrode surface, reducing the operating potential, eliminating oxygen dependence, and minimizing interference.[46,47] Ferrocene was one of the earliest discovered redox mediators used for glucose oxidase, and second-generation glucose sensors achieved significant
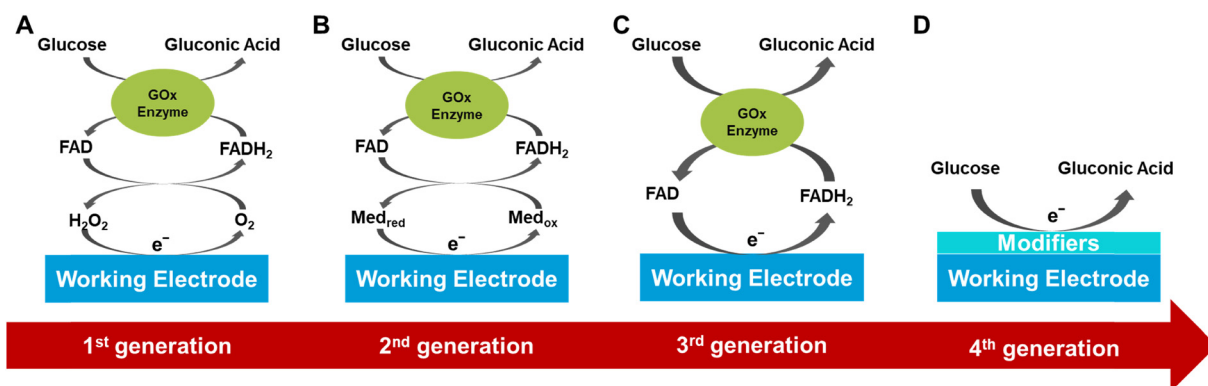
Fig. 2 Schematic representation of different generations of electrochemical glucose sensors' sensing mechanisms. (A) Classic glucose oxidase electrode sensor, (B) mediator GOx electrode sensor, (C) direct GOx electrode sensor, and (D) non-enzyme glucose sensor.

commercial success in the field of personal glucose test strips.[48] Ideal redox mediators should allow selective electrochemical reactions at lower potentials, exhibit high chemical stability, rapid response with the enzyme (relative to oxygen), and low solubility in aqueous solutions. Other common redox mediators include quinones, tetrathiafulvalene, methylene blue, ferricyanide, thionine, transition metal complexes, and ruthenium-containing redox hydrogels.[49,50] Although second-generation sensors performed well in *ex vivo* glucose testing, concerns exist regarding the leaching of redox mediators in continuous in-vivo monitoring applications, which could lead to stability and toxicity issues.

The third generation of glucose sensors eliminated the need for redox mediators and relied on direct electron transfer (DET) mechanisms.[51,52] These sensors depend on the direct electron transfer between the enzyme's active site (*e.g.*, flavin adenine dinucleotide (FAD)) and the electrode. And one of them combines a three-dimensional layered porous gold hydrogel–enzyme electrode with high biocompatibility, activity, and flexibility with high-precision, mass-producible soft-MEMS technology.[53] However, the thick insulating protein layer of the enzyme (*e.g.*, approximately 13 Å for GOx) may hinder electron transfer, resulting in a direct electron tunneling effect from the FAD redox center to the electrode.[54] Research on these sensors is ongoing, but compared to sensors based on oxygen or redox mediators, third-generation sensors have not yet been widely adopted. The main challenge of third-generation sensors lies in achieving stable direct electron transfer while maintaining the enzyme's activity and stability. Although these sensors theoretically offer higher sensitivity and specificity, their complex manufacturing processes and higher costs limit their widespread use.[55]

The fourth generation of glucose sensors, based on non-enzymatic electrodes modified with nanomaterials capable of conducting enzyme-like reactions under extreme conditions, has improved the performance of glucose sensors.[56] There have been numerous reports on non-enzymatic glucose sensors based on nanostructured metal, alloys, metal oxides, conductive polymers, MOFs, and other modified

electrodes.[57,58] The strategy designed by Li showed outstanding electrocatalytic activity and stability during glucose oxidation under neutral conditions.[59] Although enzymatic glucose sensors have successfully addressed the oxygen issue, concerns about the stability of natural enzymes remain. Non-enzymatic glucose sensors have several advantages over enzymatic sensors, including cost-effectiveness, high sensitivity, and long-term stability.[60] However, the performance of metal-based sensors can be significantly affected by the absorption of reaction intermediates during the glucose oxidation process. Therefore, the choice and structure of nanomaterials have a significant impact on the performance of non-enzymatic sensors.[61] To enhance glucose catalysis efficiency, efficient and synergistic nanomaterial combinations should be selected for glucose sensors.[50]

In summary, each generation of glucose sensors has its advantages and disadvantages. The first-generation technology is simple and cost-effective but is limited by oxygen dependence and interference issues. The second-generation technology overcomes oxygen dependence issues by introducing redox mediators but faces stability and toxicity issues related to mediator leaching. The third-generation technology, based on direct electron transfer, theoretically offers higher sensitivity and specificity but faces challenges in manufacturing and cost. The fourth-generation non-enzymatic sensor technology has stability, consistency, and selectivity issues related to nanomaterial detection of glucose. Future research efforts should focus on further optimizing these technologies to achieve more efficient, reliable, and convenient glucose monitoring.

2.2.1 Sweat-based glucose sensors. Sweat is a biological fluid secreted by the sweat glands in the skin's epidermal layer.[62] Due to its rich chemical composition and easy accessibility, it has become an attractive alternative biofluid for non-invasive biomarker monitoring associated with epidermal wearable sensing devices.[63] The glucose content in sweat is correlated with blood glucose levels, with glucose concentration in sweat varying within the 1 μM to 1 mM range.[64] The working principle is using electrochemical sensors to detect glucose content in sweat. Once collected

and corrected for individual variances, the glucose in sweat has been proven to accurately reflect the glucose level in the blood.[65] One method involves integrating a glucose sensor onto a patch, with the sensing platform directly in contact with sweat on the skin's surface.[66,67] Another method involves integrating it with a microfluidic channel containing pre-sampled sweat to transfer sweat to the sensing element.[68]

In recent years, researchers have developed several wearable sensing devices for continuous measurement of sweat glucose levels.[46] Fig. 3A shows a sweat glucose sensor integrated with a flexible self-powered watch, with the sensor conforming to the skin and directly measuring glucose in skin sweat.[69] Fig. 3B utilizes tungsten cobalt ($CoWO_4$)/CNT and polyaniline/CNT nanocomposite materials coated on a CNT–AuNS working electrode on a stretchable silicon substrate, with silver chloride nanowires serving as the reference electrode, used for wearable sweat, glucose, and pH sensing.[70] Fig. 3C displays a three-electrode electrochemical platform based on elastic gold fibers, functionalized with Prussian blue and glucose oxidase for the working electrode, and modified with Ag/AgCl as the reference electrode, maintaining good sensing performance even at 200% strain.[71] Fig. 3D reports a flexible wristband sensor array for multiplexed measurement of sweat glucose, directly connected to the skin to simultaneously measure electrolytes and metabolites, enabling measurement of body status during exercise.[72] Fig. 3E shows a wearable glucose colorimetric sensor based on a microfluidic chip, where microchannels guide sweat excreted from the skin to microchambers containing pre-embedded glucose oxidase (GOD)-peroxidase-*ortho*-phenylenediamine reagents for detecting glucose in sweat.[68] Fig. 3F demonstrates a wearable patch comprising glucose, pH, humidity, and temperature sensors, along with feedback-based drug delivery micro-needles.[73] The patch is validated for estimating actual glucose concentration in sweat during exercise and delivering diabetes medication in a mouse model. Fig. 3G transports sweat from microfluidic channels to the glucose sensor with a module for sensor signal acquisition, processing, wireless transmission, and data display, demonstrating high stability over 10 hours.[74] Fig. 3H introduces pH and temperature correction to accurately estimate sweat glucose concentration in the microfluidic device. Patch-type sweat sensors typically use soft materials attached to the skin surface, enabling direct contact with sweat and measurement of the concentration of biomolecules in it.[75]

These patch-type sensors are suitable for prolonged wear, offering good comfort and durability, but may experience displacement or detachment in highly dynamic environments. Microfluidic sensors use microfluidic channel structures for precise control of sweat collection and analysis, enabling finer and controllable sample processing, achieving higher detection sensitivity and selectivity with high accuracy and stability. The advantage of sweat glucose monitoring technology lies in its non-invasive nature, allowing continuous monitoring at home or in daily life without the discomfort associated with traditional fingerstick blood sampling. However, sweat glucose monitoring technology is not suitable for all populations. For example, for individuals with dry skin or those who do not sweat easily, the glucose content in sweat may not accurately reflect blood glucose levels.[76] Additionally, the glucose content in sweat does not always perfectly match blood glucose levels, indicating the need for further research and improvement to enhance the technology's accuracy and reliability.

2.2.2 ISF-based glucose sensors. Extracting interstitial fluid (ISF) from subcutaneous tissue to monitor blood glucose presents an appealing method for glucose detection.[77,78] ISF closely correlates with biomarker concentrations in blood, providing reliable diagnostic information.[79] The methods for accessing ISF include reverse iontophoresis (RI) and microneedle (MN) technology. RI induces iontophoretic flow by applying a weak electric current (0.2–0.5 mA cm^{-2}) to the skin, promoting the migration of ions, analytes, and metabolites.[80] Due to the negative charge of the skin physiologically, positively charged and neutral ions migrate to the cathode, while negatively charged molecules migrate to the anode. Glucose molecules have a neutral charge, thus they are collected for quantitative analysis on the cathode side during RI. Microneedle technology uses micro-scale needles to directly or indirectly (post-extraction sensing) monitor glucose concentration in ISF.[81]

In the year 2000, researchers conducted a study on the collection of ISF using reverse iontophoresis for glucose detection (Fig. 4A).[82] After applying a current of 0.25 mA cm^{-2}, glucose from ISF was extracted into a sensing unit containing buffered saline solution. In 2011, the most convenient and practical microneedle-assisted glucose detection format based on two-component assembly was introduced, creating enzyme electrodes by immobilizing glucose oxidase and poly(aniline) conducting polymer film on a solid microneedle electrode (Fig. 4B).[83] Fig. 4C shows an integrated system of RI and electrochemical sensing using a graphene miniaturized pixel array. This design utilizes channels in hair follicles to avoid sample dilution issues, enabling more accurate glucose monitoring.[84] Fig. 4D demonstrates a hollow microneedle sensing system that simultaneously monitors blood glucose and ketones, allowing for better management of diabetes by detecting multiple glucose-related biomarkers.[18] Fig. 4E presents a flexible, epidermal-wearable reverse iontophoresis glucose sensing system.[85] This system integrates ultra-thin skin-like biosensors and electrochemical dual channels powered by paper batteries, diverting blood glucose from the blood vessels to the skin surface for detection. Fig. 4F developed a multiplex sensing system for various health-related markers, providing real-time analysis of glucose, lactate, and alcohol concentrations in ISF, applicable in various scenarios such as exercise, meals, and drinking.[86]

ISF wearable sensors, using technologies like RI and microneedles, achieve the detection of biomarkers in ISF with advantages such as minimal invasiveness, effectiveness, and convenience, providing a reliable and comfortable option
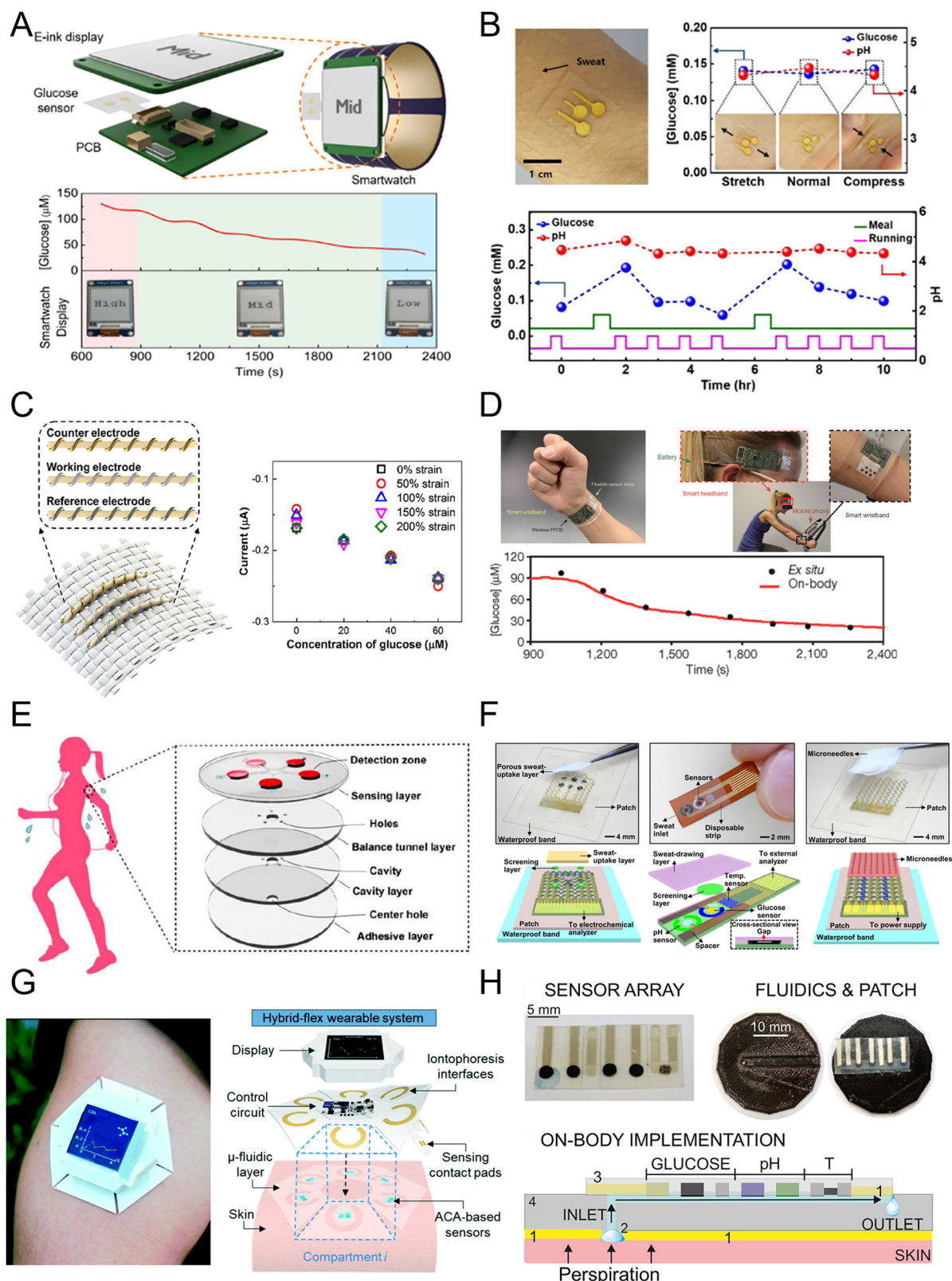
Fig. 3 Electrochemical sweat glucose sensors including (A) sensors integrated in a watch (reprinted with permission from ref. 69. Copyright 2019 American Chemical Society), (B) sensors on a flexible substrate (reprinted with permission from ref. 70. Copyright 2018 American Chemical Society), (C) stretchable glucose sensor (reprinted with permission from ref. 71. Copyright 2019 American Chemical Society), (D) multiplexed sensing platform (reprinted with permission from ref. 72. Copyright 2016 Nature Publishing Group), (E) glucose sensor patch (reprinted with permission from ref. 68. Copyright 2019 American Chemical Society), (F) closed loop sensor system (reprinted with permission from ref. 73. Copyright 2017 American Association for the Advancement of Science), (G) microfluidic glucose sensor patch (reprinted with permission from ref. 74. Copyright 2020 Royal Society of Chemistry), (H) microfluidic sensor platform (reprinted with permission from ref. 75. Copyright 2020 American Chemical Society).
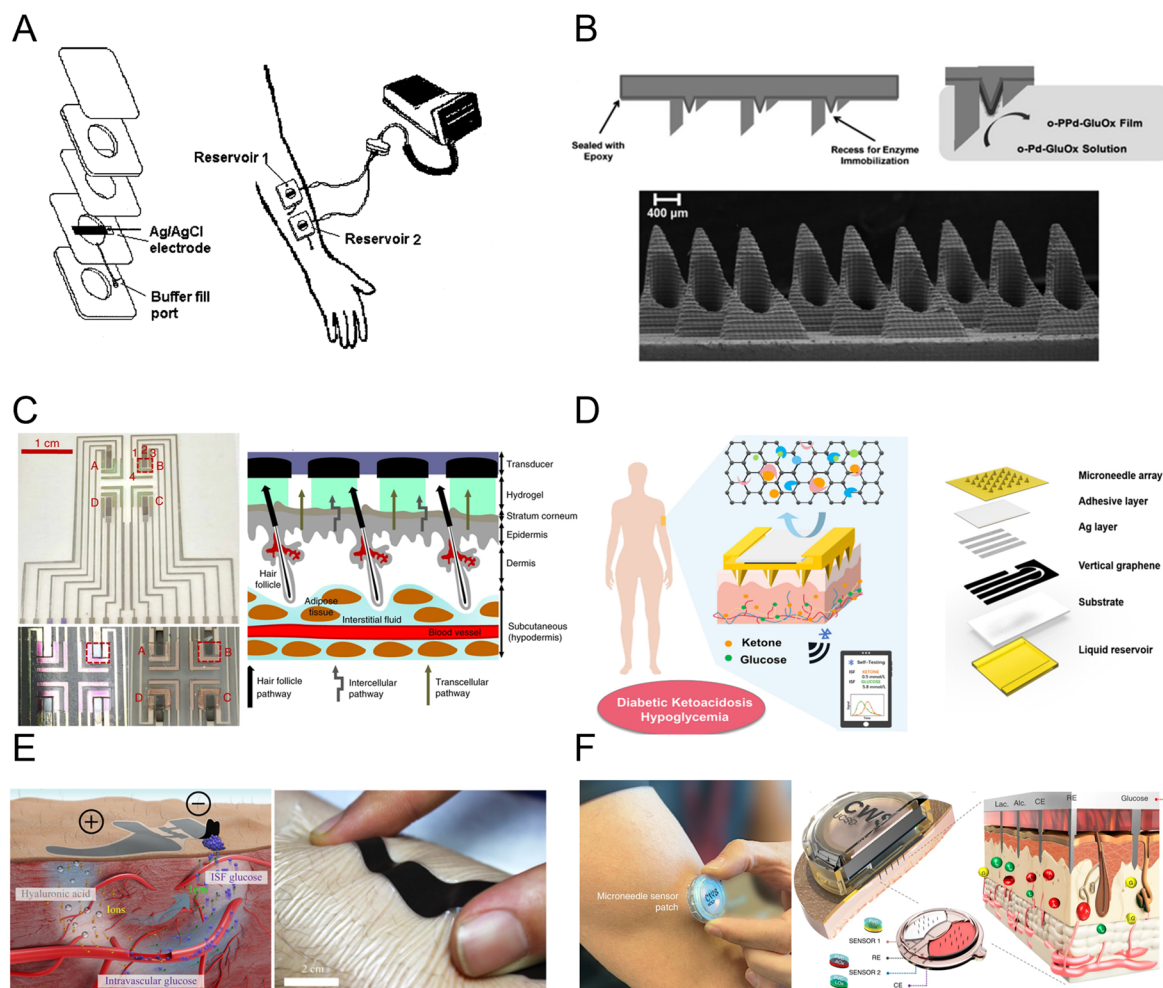
Fig. 4 Electrochemical glucose sensors based on interstitial fluid (ISF). (A) First reverse iontophoresis (RI)-based glucose sensor (reprinted with permission from ref. 82. Copyright 2000 Wiley Inc.), (B) bicomponent microneedle (MN) array glucose sensor (reprinted with permission from ref. 83. Copyright 2011 Wiley Inc.), (C) fully integrated RI glucose sensing system (reprinted with permission from ref. 84. Copyright 2018 Springer Nature), (D) MN-based glucose and ketone sensors (reprinted with permission from ref. 18. Copyright 2024 American Chemical Society), (E) skin-like RI-based glucose sensor patch (reprinted with permission from ref. 85. Copyright 2017 American Association for the Advancement of Science), (F) multiplexed MN-based sensing system for glucose, lactate, and alcohol monitoring (reprinted with permission from ref. 86. Copyright 2022 Springer Nature).

for glucose monitoring. Although ISF-based glucose detection technologies demonstrate tremendous potential for glucose monitoring, they still face challenges in commercial applications, such as the need for hydrogel membranes in RI to avoid direct contact between the skin and the iontophoresis region, as well as the potential skin irritation and discomfort associated with RI and MN.

2.2.3 Tear-based glucose sensors. Tears, as a non-invasive body fluid for glucose monitoring, are an attractive option due to their easy accessibility, continuous flow, and the correlation between tear glucose and blood glucose mediated by diffusion from the lacrimal artery.[87] Based on these characteristics, the development of wearable tear glucose sensors has garnered widespread attention.[88] Tear glucose sensors are primarily based on optical and electrochemical detection, with advantages such as rapid response, high sensitivity, and accuracy.[89]

Early designs of tear glucose sensors aimed to achieve flexible and miniaturized structures to ensure user safety and comfort, since the eye is a delicate organ.[14] In 2011, Parviz's team first described an electrochemical contact lens for tear glucose detection, as shown in Fig. 5A.[90] This sensor composes of a transparent and soft polyethylene terephthalate substrate, titanium/palladium/platinum metal layers, and a titanium dioxide sol–gel membrane immobilized with glucose oxidase, exhibited high sensitivity and a good linear range with a detection limit below 0.01 mM. Fig. 5B presents a tear-based sensor developed using a graphene–silver nanowire hybrid structure in a non-invasive manner. This structure improved electrical and mechanical properties, and the transconductivity of this hybrid structure was minimal, rendering it suitable for use as an electrode in the fabrication of passive electronic components.[91] Google and Novartis proposed developing a smart contact lens for
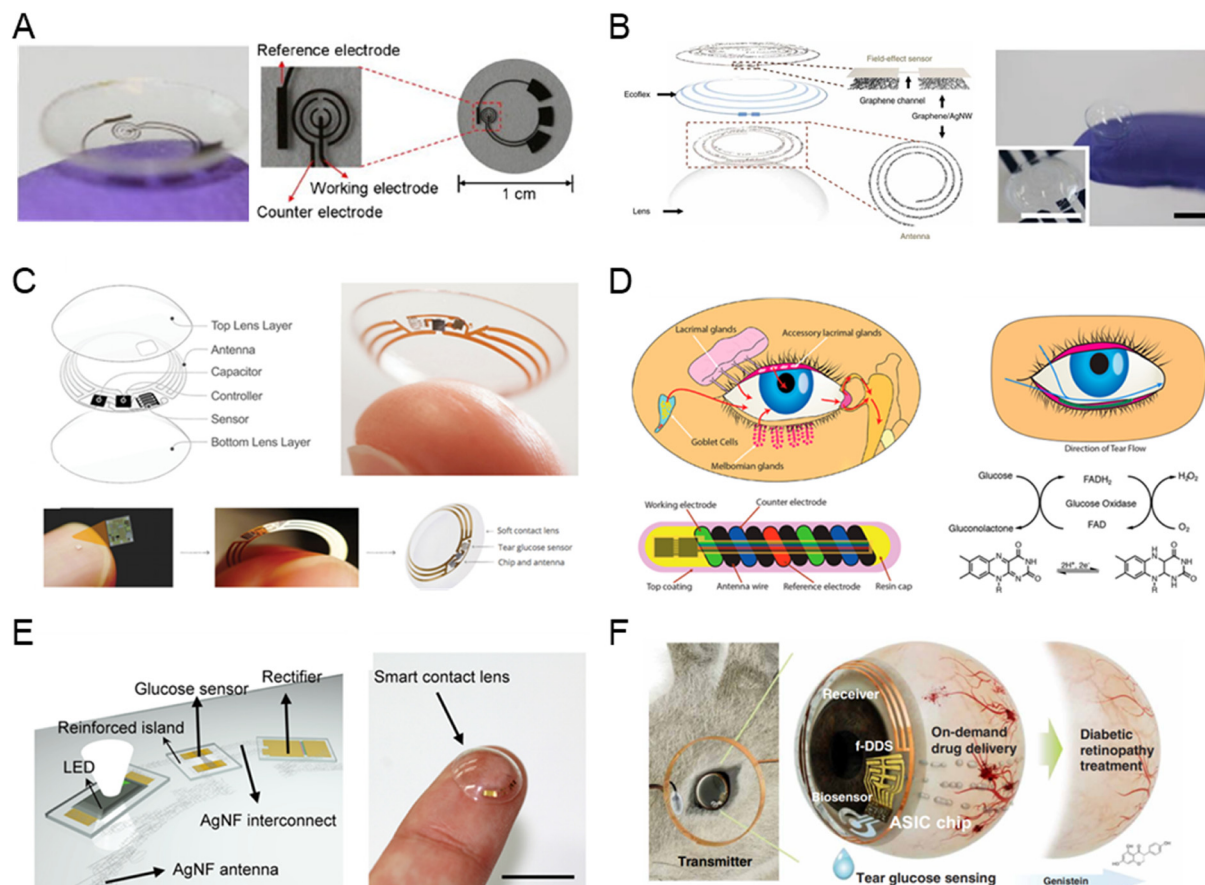
Fig. 5 Tear-based glucose sensor. (A) An electrochemical glucose sensor integrated on a contact lens (reprinted with permission from ref. 90. Copyright 2011 Elsevier.), (B) graphene–silver nanowire based glucose sensor (reprinted with permission from ref. 91. Copyright 2017 Springer Nature.), (C) Google X's smart contact lens (images adapted from **https://sites.google.com/site/smartcontactlens/**. Reprinted with permission from ref. 92. Copyright 2015 WILEY-VCH Verlag GmbH & Co.), (D) spring-like glucose sensor developed by NovioSense (reprinted with permission from ref. 93. Copyright 2018 American Chemical Society), (E) contact lens for real-time glucose sensing integrated with LED for data feedback (reprinted with permission from ref. 94. Copyright 2018 American Association for the Advancement of Science), (F) contact lens for glucose detection and on-demand drug delivery (reprinted with permission from ref. 95. Copyright 2020 American Association for the Advancement of Science).

continuous tear glucose monitoring, as shown in Fig. 5C.[92] However, due to a lack of supporting evidence on the correlation between tear and blood glucose, the project was halted in 2018. NovioSense developed a spring-like miniaturized tear glucose sensor, reporting accuracy comparable to commercial CGM devices in phase II clinical trials, as shown Fig. 5D.[93] Fig. 5E presents an integrated sensor combining glucose detection and intraocular pressure measurement.[94] The smart contact lens, incorporating an LED display, enabled real-time tear glucose readings by switching off the LED when glucose levels in tears reached a threshold. Fig. 5F developed smart contact lenses can noninvasively monitor glucose levels in tears and deliver on-demand drugs for diabetic retinopathy treatment.[95]

Although the field of tear glucose sensors has progressed rapidly, certain barriers must be addressed before practical application. Firstly, sensor safety is a primary concern, necessitating toxicity evaluation for human use. Additionally, the optical transparency and mechanical stretchability of the sensors require further optimization. Power supply also remains an issue, as many devices rely on external power sources, highlighting the future need for self-powered smart contact lenses. Finally, large-scale validation studies are essential to establish the correlation between tear and blood glucose concentrations.

2.2.4 Saliva-based glucose sensors. Saliva has emerged as a strong candidate for non-invasive monitoring because it can be easily accessed without the need for skin punctures or causing adverse effects.[96,97] It contains a variety of substances, including secretions from salivary glands, microbial components, and blood constituents that permeate through intercellular or transcellular pathways.[98] As a result, the concentrations of analytes in saliva often correlate with those found in blood.[99] However, it's important to note that the concentrations of these analytes in saliva are typically lower, despite saliva samples being generally larger than other fluids, such as interstitial fluid or blood.[100] These characteristics, along with its accessibility and compositional diversity, position saliva as a valuable focus in fields such as biomedicine, nutrition, and health monitoring.

As early as 1991, elevated glucose levels were observed in the saliva samples of diabetic patients, which opened up the possibility for non-invasive monitoring that avoids traditional needle pricks and blood draws.[17] The wearable device designed to estimate salivary glucose was developed in the form of a salivary biosensor integrated into a mouthguard, as shown in Fig. 6A.[101] This sensor consists of a platinum electrode modified with glucose oxidase, which detects glucose in artificial saliva through electrochemical methods. This allows for real-time, non-invasive glucose monitoring *via* a wireless measurement system. Fig. 6B illustrates a mouthguard biosensor specifically designed for non-invasive monitoring of salivary glucose. The biosensor is constructed on the surface of a mouthguard made from dental polyethylene terephthalate glycol (PETG), achieving high sensitivity for detecting the range of human salivary glucose levels.[102] Fig. 6C presents a novel method for oral glucose detection, which involves a modified membrane that is sensitive to changes in pH, temperature, and glucose

levels.[103] This membrane was placed between two resonators and demonstrated by being attached to a human tooth. The sensor, based on a broadside-coupled split-ring resonator, includes a silk membrane along with a responsive hydrogel layer. The hydrogel expands by absorbing surrounding solvents, altering its thickness and dielectric constant, which in turn changes the resonance frequency and signal amplitude. This frequency shift in response to the presence of glucose highlights the sensitivity of the functionalized membrane to biomolecules such as glucose.

Detecting glucose in saliva with small wearable devices has the potential to create non-invasive methods for accessing biofluid data and detecting other analytes. However, challenges such as interference from food, device damage during eating, and sensor stability due to biofouling remain. User comfort is vital, as oral devices can be uncomfortable. While mouthguard-based sensors are beneficial for athletes, they are often impractical for daily use. Integrating devices into dental prosthetics or children's
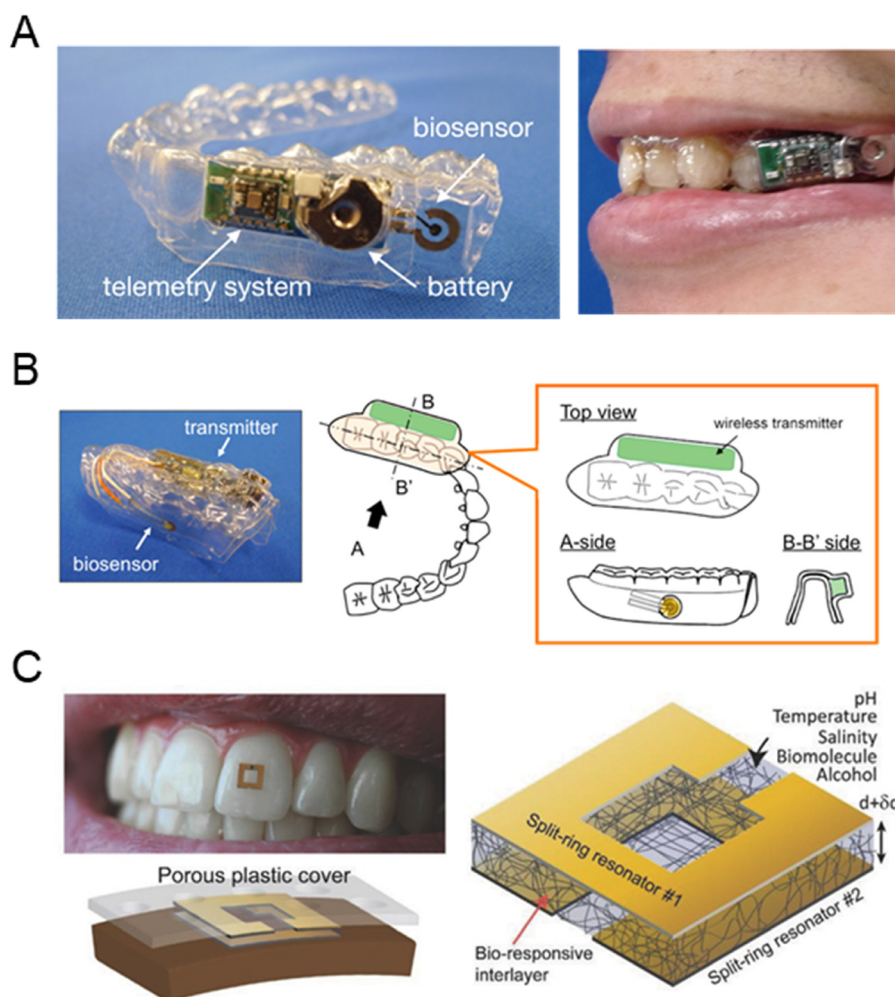
Fig. 6 Saliva-based glucose sensor. (A) Wearable device for saliva glucose estimation (reprinted with permission from ref. 101. Copyright 2020 American Chemical Society), (B) mouthguard biosensor with telemetry system for glucose monitoring (reprinted with permission from ref. 102. Copyright 2016 Elsevier.), (C) wearable sensor on human teeth for the detection of biomolecules (reprinted with permission from ref. 103. Copyright 2018 Wiley-VCH Verlag GmbH & Co).

pacifiers offers a more comfortable solution. Future advancements should focus on miniaturizing these devices and enabling autonomous operation without external power, facilitating continuous glucose monitoring. Additionally, large-scale studies are necessary to accurately correlate saliva and blood glucose levels.

2.3. Optical methods

Optical sensors have emerged as a promising platform for non-invasive glucose monitoring, offering distinct advantages over traditional electrochemical biosensors by utilizing photon detection rather than electron transfer mechanisms.[104] These sensors allow for continuous, real-time monitoring of glucose levels in biofluids through techniques such as near-infrared, mid-infrared, fluorescence, and Raman spectroscopy. Their ability to provide label-free, noninvasive detection with internal calibration has garnered significant attention, positioning optical sensors as a critical technology for developing reliable, user-friendly, and continuous glucose monitoring systems.[105]

2.3.1 NIR/MIR spectroscopy. In non-invasive blood glucose monitoring, near-infrared (NIR, 680–2500 nm) and mid-infrared (MIR, 2500–25 000 nm) wavelengths provide relatively ideal detection spectra,[46] since ultraviolet light can be easily absorbed by DNA and proteins, while visible light is primarily absorbed by hemoglobin, and infrared light is absorbed by water.[106] This allows for the analysis of molecular vibrations and rotations, leading to glucose concentration estimations.[107] Analyzing these spectral features enables indirect measurements of blood glucose levels.[108]

NIR and MIR spectroscopy, due to their non-invasive nature, significantly reduce patient discomfort and offer the capability to detect minor fluctuations in glucose concentration in biofluids, thereby facilitating continuous and real-time monitoring.[109] NIR is remarkably versatile due to its ability to operate in reflection, interaction, and transmission modes. However, it faces challenges from physiological variables such as tissue thickness, temperature, and ambient light. Meanwhile, MIR spectroscopy excels in providing sharp response peaks with lower scattering, enhancing detection accuracy, but is constrained to reflection mode due to limited tissue penetration.[110] The incorporation of advanced calibration models and multivariate analysis further enhances measurement precision.[111]

Fig. 7A presents a method using NIR spectroscopy for non-invasive, rapid blood glucose measurement in diabetic and normal rats. Comparing partial least squares (PLS)
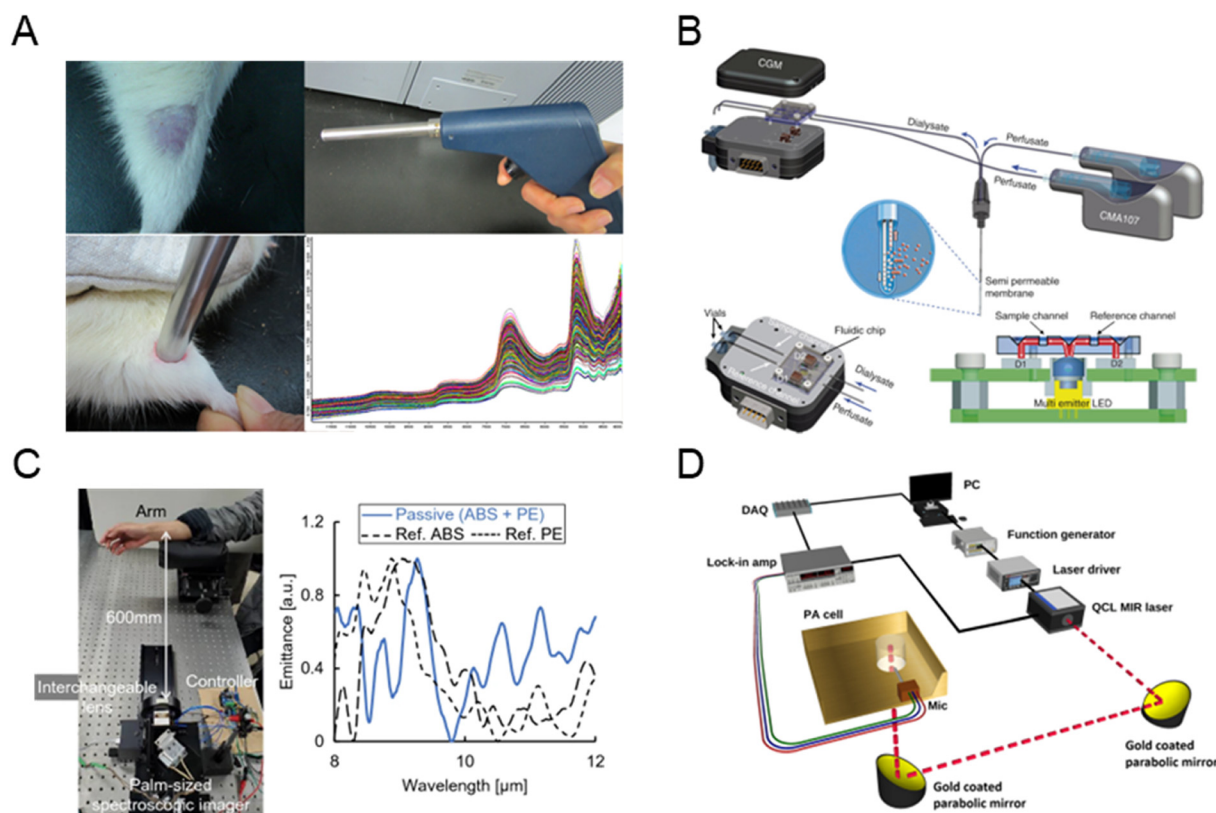

Fig. 7 NIR/MIR spectroscopy-based glucose sensor. (A) Noninvasive *in vivo* blood glucose monitoring using NIR spectroscopy. Adapted with permission.[112] Copyright 2017, Elsevier. (B) NIR sensor integrating a microfluidic chip and microdialysis for continuous glucose monitoring (reprinted with permission from ref. 113. Copyright 2014 Elsevier). (C) MIR imaging of the wrist for non-invasive glucose sensing (reprinted with permission from ref. 114. Copyright 2022 Springer Nature). (D) The setup used for glucose detection using MIR and PA spectroscopy (reprinted with permission from ref. 115. Copyright 2023 Springer Nature).

regression and artificial neural networks (ANN) showed both methods to be robust, accurate, and repeatable.[112] Fig. 7B shows a semi-invasive NIR sensor integrating a microfluidic chip and microdialysis for continuous glucose monitoring, demonstrating a detection limit of 20 mg dL^{-1} *in vitro* and a MARE of 13.8% *in vivo*.[113] As shown in Fig. 7C, MIR passive spectroscopic imaging enables remote glucose measurement by detecting glucose-induced luminescence from body thermal radiation. Wrist emission spectra correlated strongly with invasive glucose measurements over 60 minutes, offering the potential for real-time monitoring of diabetic patients to detect hypoglycemia or hyperglycemia.[114] As shown in Fig. 7D, a MIR photoacoustic system using a single-wavelength quantum cascade laser at 1080 cm^{-1} has been developed for non-invasive glucose monitoring. Tested with

artificial skin phantoms, it achieved a detection sensitivity of ±25 mg dL^{-1} across normal and hyperglycemic ranges.[115]

NIR and MIR spectroscopy techniques offer key advantages in glucose detection due to their non-invasive nature, high sensitivity, and specificity, eliminating the need for blood samples and thus reducing patient discomfort.[116] They can detect minor glucose fluctuations and distinguish between various biomolecules, minimizing interference from other substances during detection. However, these techniques face challenges, as changes in blood glucose often produce only small spectral signal variations, requiring highly sensitive instruments for accurate detection. Additionally, interference from other sample components can complicate spectral analysis, while the high costs of equipment and the necessity for specialized personnel for
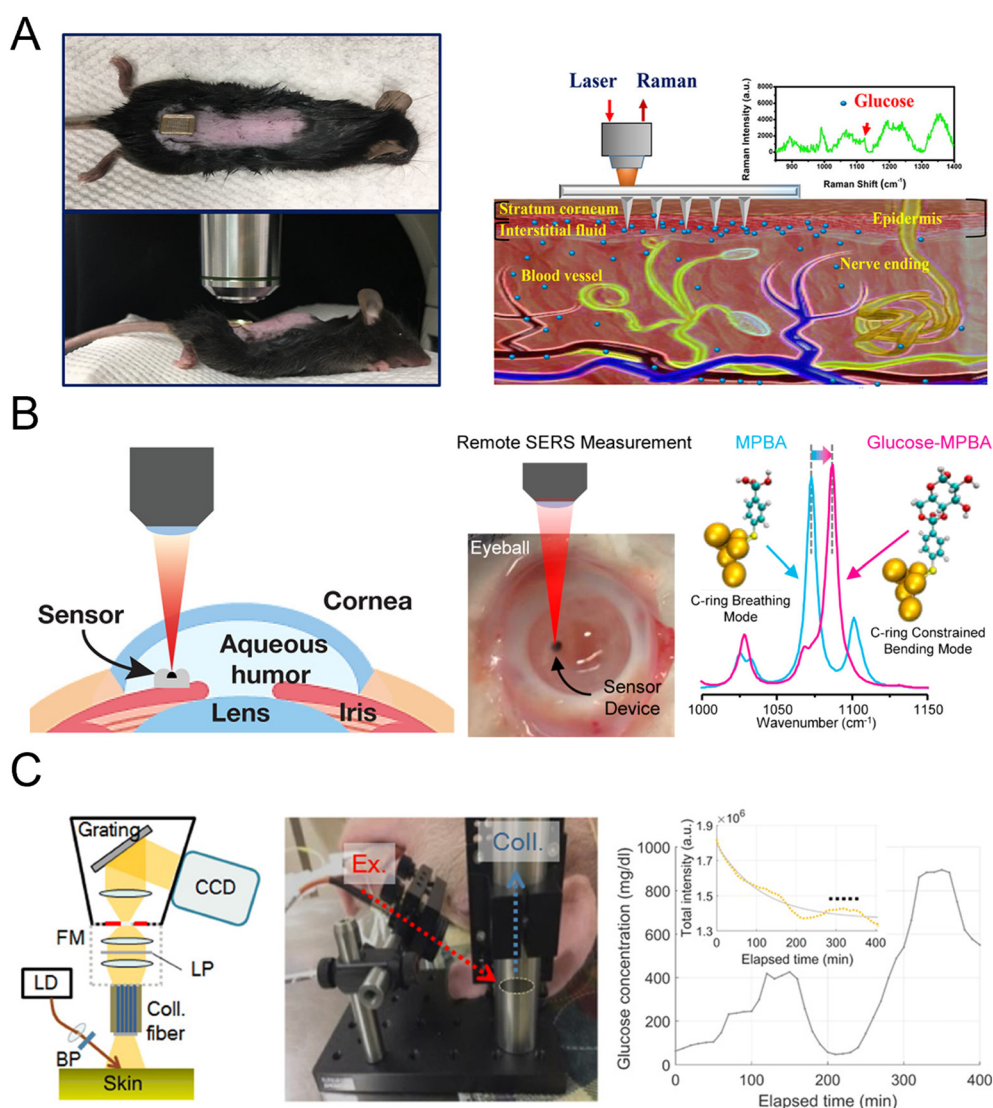
Fig. 8 Raman-based glucose sensor. (A) Surface-enhanced Raman spectroscopy using microneedle array for *in situ* glucose detection (reprinted with permission from ref. 122. Copyright 2020 American Chemical Society). (B) Continuous glucose sensing using SERS emission shifts (reprinted with permission from ref. 123. Copyright 2018 American Chemical Society). (C) Direct observation of glucose fingerprint using *in vivo* Raman spectroscopy (reprinted with permission from ref. 121. Copyright 2020 American Association for the Advancement of Science).

operation and data analysis present further obstacles to widespread clinical use.[117]

2.3.2 Raman spectroscopy. Raman spectroscopy for non-invasive measuring blood glucose concentration is based on the changes in the frequency of scattered light caused by glucose.[118] Its principle involves using a laser to illuminate the sample, which produces a Raman scattering spectrum.[119] Specifically, when exposed to laser light, glucose molecules in the blood will vibrate and rotate, producing a distinct Raman spectrum with various peaks corresponding to different molecular vibration modes, such as C–C and C–H bonds.[21] By measuring the intensity and frequency of these Raman peaks, the blood glucose concentration in the sample can be inferred.[120] Due to the unique Raman spectral lines of glucose, this method provides high measurement accuracy.[121] However, the glucose signal can be easily masked by the signals from collagen and triglycerides in the dermis.

Fig. 8A presents a surface-enhanced Raman spectroscopy (SERS) sensor using a low-cost poly(methyl-methacrylate) (PMMA) microneedle array for *in situ* intradermal glucose detection, calibrated in skin phantoms and tested in diabetic mice.[122] The sensor demonstrated rapid glucose measurement in interstitial fluid with minimal invasiveness, showing potential for painless glucose monitoring in diabetic patients. Fig. 8B illustrates fast and continuous glucose sensing using SERS emission shifts of mercaptophenylboronic acid (MPBA), demonstrating reversible MPBA–glucose bonding for stable performance over 30 days in the physiologically relevant range.[123] This approach was further validated through intraocular glucose measurements in *ex vivo* rabbit eyes, achieving accuracy within ±0.5 mM of commercial sensors. Fig. 8C demonstrates the direct observation of glucose-specific Raman peaks in swine glucose clamping experiments, confirming a linear relationship between Raman peak intensities and reference glucose concentrations.[121] A robust prediction method for glucose concentration, incorporating both glucose and skin-related Raman peaks, was developed and tested across single and multiple subject recordings.

The advantages of the Raman spectroscopy blood glucose detection technique include non-invasiveness, high sensitivity, and high specificity. Since it does not require blood samples, it minimizes discomfort for patients and is capable of detecting minute changes in glucose concentration. Furthermore, Raman spectroscopy's high specificity allows it to distinguish between different biomolecules, thereby reducing interference from other substances in the detection results.[124] However, there are challenges associated with Raman spectroscopy for blood glucose detection. First, the relatively low concentration of glucose in the blood necessitates highly sensitive instruments to detect weak Raman signals. Additionally, interference from other components in the sample may affect the interpretation of Raman spectra and the accuracy of glucose measurements. Moreover, Raman spectrometers are expensive and require trained personnel for operation and data analysis, which limits their wider adoption and application in clinical practice.[125]

2.3.3 Optical coherence tomography (OCT). Optical coherence tomography (OCT) is a promising non-invasive technique for monitoring blood glucose levels using optical interference principles.[126] Coherent light is directed onto the skin, and the backscattered light interacts with a reference signal to produce an interference pattern. By analyzing this pattern, OCT provides insights into tissue reflectivity and scattering, enabling the indirect estimation of glucose concentrations.[127] Changes in glucose levels alter the refractive index and decrease the scattering coefficient, offering measurable optical markers for glucose monitoring.[128]

The advantages of OCT include its non-invasive nature, high spatial and temporal resolution, real-time monitoring capability, and depth-resolving ability, making it suitable for various tissue types. These features allow OCT to detect glucose at different tissue layers, theoretically unaffected by physiological factors such as heart rate, blood pressure, osmolytes, or red blood cell concentration.[129] However, the subtle effect of glucose concentration on optical properties poses a significant challenge, requiring highly sensitive equipment to detect minor signal variations. Furthermore, tissue-specific optical characteristics, such as vascular density and refractive index, along with motion artifacts and temperature fluctuations, can compromise measurement accuracy. While OCT offers depth-resolved glucose monitoring, these limitations hinder its development into reliable continuous monitoring devices. High equipment costs and the need for precise calibration further restrict its broader clinical adoption.[130]

2.3.4 Optical polarimetry (OP). Optical polarimetry for blood glucose detection is a non-invasive technique that relies on the optical rotation effect.[131] This method measures changes in the optical rotation angle of polarized light passing through a sample to indirectly infer blood glucose levels. In this approach, glucose molecules in the blood interact with optically active substances, causing a shift in the rotation angle of polarized light. By measuring this change in optical rotation, glucose concentrations in the blood can be estimated.[132]

The advantages of optical polarimetry for glucose monitoring include non-invasiveness, ease of use, and real-time results. It reduces patient discomfort by eliminating the need for blood samples, making it suitable for both clinical and home settings. Additionally, this method requires minimal sample preparation and can work with various biological samples. However, there are challenges.[133] Other blood components, such as hemoglobin and cholesterol, can interfere with optical rotation measurements. Since glucose-induced changes in optical rotation are minor, highly sensitive equipment is needed to detect these subtle shifts. The technology is also costly and can be affected by environmental factors like light intensity and temperature, which may impact measurement accuracy and stability. Further research is needed to reduce delay times and address the technique's high sensitivity to movement, temperature, interfering compounds, and pH levels.[134]

2.3.5 Fluorescence. Fluorescence-based glucose sensing relies on fluorophores emitting light at specific wavelengths after absorbing radiation, with fluorescence intensity or decay time correlating to glucose concentration.[135] To enhance selectivity and reversibility, intermediary molecules like enzymes, boronic acid derivatives, or quantum dots (QDs) are used, enabling techniques such as fluorescence resonance energy transfer (FRET) or ratiometric sensing.[136]

Advanced designs, including carbon dots (CDs), fluorescent probes, and dual enzymatic reactions,

improve sensitivity and allow glucose quantification in biofluids like blood and tears. These methods leverage changes in fluorescence ratios caused by glucose oxidation products, offering high sensitivity, specificity, and visual feedback, with detection limits reaching as low as 0.08 μM. While ratiometric fluorescence biosensors provide gradient visual feedback for glucose levels, quantitative precision remains a challenge for further development.[137]

Fig. 9A presents a fluorescent and colorimetric glucose sensor using metal oxide hybrid nitrogen-doped carbon dots
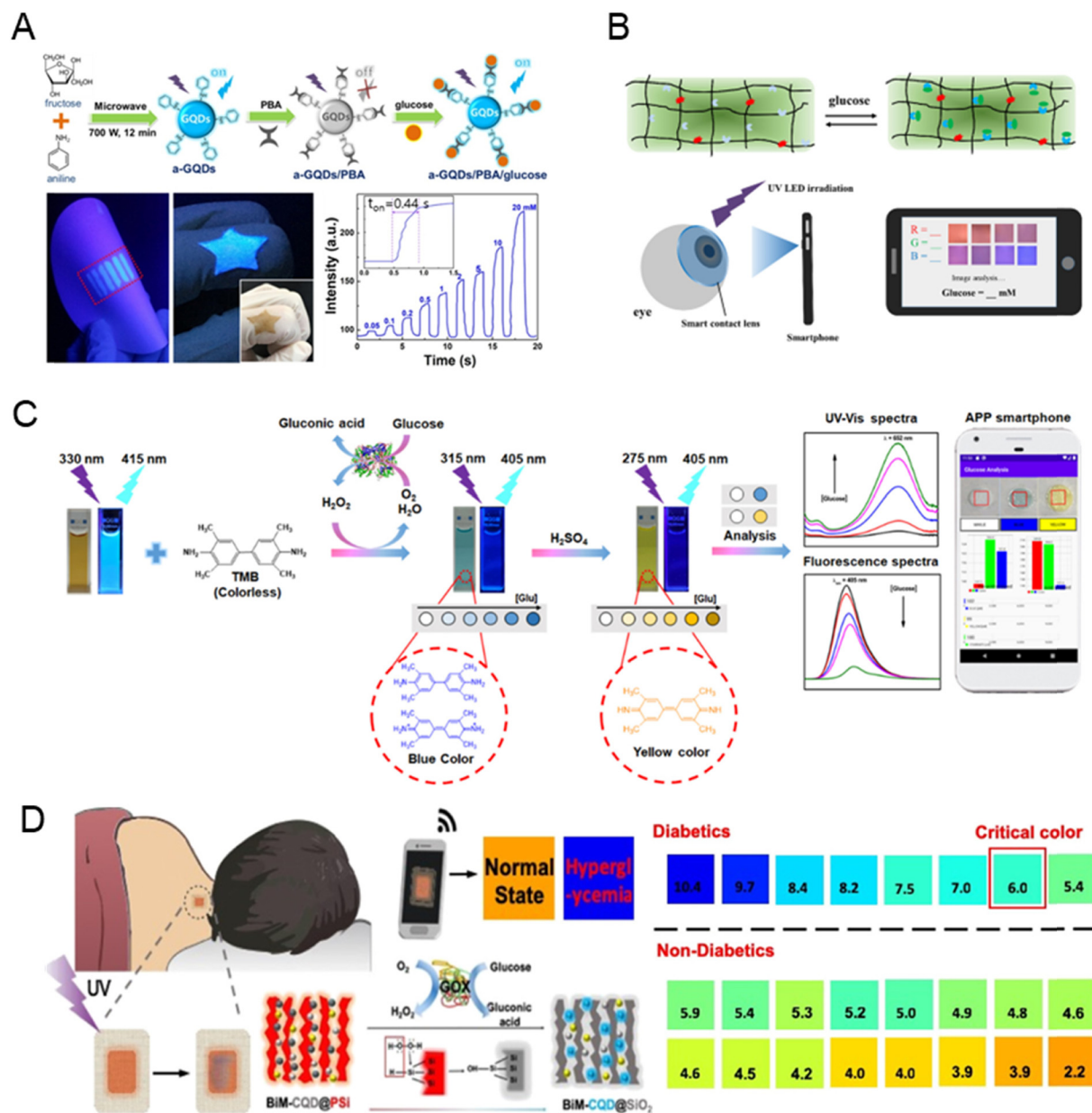
Fig. 9 Fluorescence-based glucose sensor. (A) Paper- and fiber optic-based fluorescent sensor for glucose detection (reprinted with permission from ref. 138. Copyright 2021 Elsevier), (B) wearable fluorescent contact lenses for monitoring glucose (reprinted with permission from ref. 139. Copyright 2022 Elsevier). (C) Paper-based colorimetric and fluorescent glucose sensor (reprinted with permission from ref. 140. Copyright 2021 Elsevier), (D) ratiometric fluorescent nanohybrid for sweat glucose monitoring (reprinted with permission from ref. 141. Copyright 2020 Americal Chemical Society).

(MFNCDs), leveraging their peroxidase-like activity to catalyze glucose oxidation and enable quantitative detection with high sensitivity. The sensor exhibited excellent biocompatibility, low cytotoxicity, and potential for on-site glucose analysis *via* smartphone integration, making it suitable for real serum applications.[138] Fig. 9B shows smart contact lenses with flexible hydrogels have been developed for real-time, non-invasive glucose monitoring in tears, utilizing a glucose-sensitive fluorescent probe to detect concentrations ranging from 23 μM to 1.0 mM. The lenses enable smartphone-based RGB signal quantification, offering a biosafe and painless platform for continuous glucose monitoring.[139] As shown in Fig. 9C, aniline-functionalized graphene quantum dots (a-GQDs) modulated with phenyl boric acid (PBA) were developed as a fluorescent glucose sensor, offering high sensitivity and selectivity through fluorescence quenching. The sensor's versatility was demonstrated with paper-based devices for portable glucose detection, fiber optic sensors for fast on-site applications, and wearable hydrogel films, all showcasing excellent performance and biocompatibility.[140] In Fig. 9D, a wearable skin pad based on a ratiometric fluorescent nanohybrid has been developed for non-invasive, visual monitoring of sweat glucose, utilizing a red-to-blue fluorescence transition triggered by glucose oxidation. This biocompatible device demonstrates a strong correlation between fluorescence change and sweat glucose levels, enabling accurate detection of hyperglycemia in clinical tests.[141]

However, challenges exist, such as cell or protein buildup around the sensor or fibrous encapsulation post-implantation, which can reduce sensor accuracy and eventually cause it to fail *in vivo*. Enhancing the biocompatibility of these miniature biosensors remains a key focus in advancing implantable sensor technology.

Fluorescence glucose detection also has potential for commercial applications. Its operation involves fluorescent probes that either enhance or quench fluorescence when binding with glucose molecules, allowing quantitative glucose analysis through fluorescence signal changes.[142] Commercially, several fluorescence-based glucose monitoring products are available, including portable devices and earring-style monitors, providing convenient glucose monitoring options for users.

This technology offers accurate glucose monitoring, with specific fluorescent probes ensuring high sensor specificity. Fluorescent materials like quantum dots and carbon dots are also commonly used in glucose detection, providing high fluorescence efficiency and photostability, which help enhance the accuracy and consistency of measurements.[143] Yet, challenges remain. The accuracy and stability of fluorescence glucose detection still need improvement, especially as dynamic glucose changes can introduce errors. Environmental factors, such as light intensity and temperature, can affect the fluorescence signal and impact measurement accuracy. Additionally, the high cost of some commercial fluorescence-based glucose monitors may limit broader accessibility and adoption.

2.4. Other methods

2.4.1 Millimeter-wave (mmW) and microwave (MW).
Millimeter wave (mmW) and microwave (MW) technologies are emerging techniques for non-invasive glucose monitoring.[144,145] These methods utilize specific frequency ranges in the electromagnetic spectrum, particularly within dielectric spectroscopy. The frequencies used can penetrate deep into tissue, overcoming the limitations of optical methods, and enable accurate glucose detection through their interaction with glucose molecules. Glucose interacts with electromagnetic waves in various ways, including reflection, transmission, vibration (in resonant systems), and radar effects, depending on the frequency employed. This interaction allows for the determination of glucose concentration based on changes in energy levels.[146]

The main advantages of mmW and MW sensing techniques include high sensitivity, rapid response times, flexibility, low power consumption, portability, and ease of manufacture.[147] These technologies do not require precise alignment and are cost-effective for real-time measurements. The mmW spectrum, particularly between 30 and 300 GHz, has shown promise for *in vivo* glucose monitoring through skin tissue, with certain frequency bands proving to be particularly effective.[148]

However, it's important to note that while mmW and MW techniques are promising, their penetration depth could potentially cause tissue damage with repeated exposure, which limits their usefulness for continuous glucose monitoring.[149] These sensing methods rely on the dielectric properties of biological tissues, which vary with fluctuations in glucose levels. Key interactions that enable glucose concentration detection include reflection, transmission, absorption, and resonant perturbation. Advances in micro-fabrication techniques are enhancing sensor designs, improving their sensitivity and accuracy. Nonetheless, challenges remain, such as the impact of environmental factors (like temperature and movement) and variations in tissue, necessitating ongoing refinement for practical and reliable glucose monitoring.

2.4.2 Ultrasound.
The ultrasound method for non-invasive glucose monitoring utilizes the propagation time of ultrasound waves through biological media, where variations in glucose concentration influence wave speed.[150,151] Specifically, increased glucose levels result in faster transmission speeds due to changes in acoustic impedance, which is affected by the density and compressibility of the tissue. This method offers several advantages, including the ability to penetrate deep into tissues, high sensitivity, and resilience to variations in skin color, making it a promising technology for glucose monitoring.

While the ultrasound technique has limitations, such as high costs and sensitivity to temperature and pressure fluctuations, it remains a compelling option. The integration of ultrasound with other techniques, particularly near-infrared spectroscopy, enhances its potential for accurate and reliable

glucose monitoring.[152] Additionally, advancements in ultrasound-assisted mid-infrared spectroscopic imaging, which generates standing waves to create a reflective plane at a depth of approximately 100 micrometers, help mitigate issues related to water absorption and ultrasound attenuation. Despite these advancements, the impact of environmental temperature on measurement accuracy continues to pose challenges. Ongoing research and refinement are essential to improve the precision and reliability of this method for practical applications in glucose monitoring.[153]

2.4.3 Bioimpedance spectroscopy. Bioimpedance spectroscopy (BIS) measures glucose levels by applying an alternating electrical current to the skin and analyzing the resulting voltage or conductivity.[153] At low frequencies (less than 5 kHz), BIS measures impedance, which includes resistance and reactance, as the electrical current interacts with various tissues and fluids. It detects changes in electrical properties, such as blood volume or the conductivity of red blood cells (RBCs), which are affected by variations in glucose concentration.[154] These fluctuations are connected to changes in sodium (Na^+) and potassium (K^+) ion concentrations in plasma, which alter the permittivity and conductivity of RBC membranes.[155]

BIS has several advantages, including being inexpensive, safe, reliable, fast, and compact, making it suitable for wearable applications. Recent advancements include the development of a biocompatible wearable ring and wrist device that can collect bioimpedance data while compensating for skin temperature and motion, addressing traditional challenges related to instability from sweat or movement.[156] However, BIS also faces limitations, such as the difficulty in accurately predicting cell impedance due to cell membrane capacitance and sensitivity to external factors like sweat and temperature fluctuations. Despite these challenges, BIS shows promise as an accurate, real-time, and continuous glucose monitoring technique, especially with ongoing innovations in wearable device design aimed at enhancing stability and precision.[157]

3. Commercial products

The early reverse iontophoresis technology began in the early 2000s. Researchers used Plexiglas blocks to simulate the geometric structure of water gel pads for extracting glucose from interstitial fluid. By applying a current density of 0.25 mA cm^{-2} for 15 minutes, glucose was successfully extracted from the ISF into a sensor unit containing a buffered saline solution, and was detected electrochemically using an enzyme biosensor. This preliminary research laid the foundation for further development of non-invasive monitoring platforms. The GlucoWatch Biographer developed by Cygnus, Inc. was the first commercially approved non-invasive continuous glucose monitoring device by the FDA. The device integrates two conductive terminals, two gel pads loaded with glucose oxidase, a temperature sensor, a skin conductivity sensor, and an electrochemical sensor. It

samples glucose from the ISF every 20 minutes for up to 12 hours. While the GlucoWatch showed good correlation in blood glucose monitoring, its long warm-up time (2–3 hours), daily calibration requirement, and inability to effectively detect hypoglycemic events in infants led to its market withdrawal. In recent years, the Wizmi™ NIR device has employed near-infrared spectroscopy (NIR) technology to measure blood glucose levels on wrist skin. In a prospective clinical trial, this technology demonstrated good system accuracy and high precision data among 32 healthy pregnant women.[158] Additionally, the Tensor Tip CoG NIR device also uses NIR technology but measures blood glucose levels on fingertip skin. Although specific data has not been disclosed, this technology has achieved positive results in validating system accuracy.[159] The C8 RI device offers convenient non-invasive blood glucose monitoring through the skin at the waist, but lacks specific technical details and clinical trial data.[160] In contrast, the Gluco Beam™ RI provides high accuracy blood glucose data by measuring ISF at the fingertip for diabetic patients.[161] This device utilizes ISF measurement technology and has shown good accuracy in practical clinical applications. The GlucoWatch G2 RI device can measure ISF on the wrist and provide continuous blood glucose data suitable for children and diabetic patients, with its performance validated in multiple clinical studies.[162] The Sugar Beat™ RI adopts patch technology for minimally invasive measurements in ISF, suitable for diabetic patients, and has displayed MARD values ranging from 8% to 17%, meeting the standards for minimally invasive blood glucose monitoring.[163] There are also devices that utilize other principle technologies for blood glucose measurement, which perform well. For example, the Gluco Track device combines electromagnetic waves, ultrasound, and multiple technologies to provide highly accurate blood glucose measurements and demonstrates good system accuracy.[164] The Novio Sense device measures blood glucose in tear fluid using enzymatic methods to reduce discomfort for patients, targeted at certain diabetic patients.[165] The Gluco Track from Integrity Applications Ltd. (Ashdod, Israel) and the egm1000™ earlobe device from Evia Medical Technologies Ltd. (Webridge, UK) aim to intermittently estimate blood glucose levels in type 2 diabetes patients, combining three different technologies, including ultrasound, electromagnetic RF waves, and thermography. Specifically, the egm1000™ has obtained CE certification and is currently available for purchase.[166] The combination of multiple technologies can significantly enhance accuracy by reducing the chances of error and identifying and implementing corrections for environmental or physiological parameters that affect accuracy, both benefiting from advancements in machine learning to improve precision. The NIRLUS device offers high accuracy blood glucose measurement suitable for healthy individuals and diabetic patients.[167] However, in multiple studies, this device showed MARD values of approximately 8% to 17% among diabetic populations; although in line with minimally invasive CGM levels, overall accuracy still needs improvement

to better fit the requirements of different blood glucose ranges and populations. Clinical applications of sweat glucose monitoring technology in recent years, several companies and research teams have been dedicated to developing sweat glucose monitoring technology, which offers a painless, non-invasive method of monitoring blood glucose levels by detecting glucose levels in sweat. For instance, Persperion, a licensed company that has secured $4 million in seed funding, is developing a sensor that detects blood glucose through sweat, aiming for market launch in the coming years. Although current technologies need further research and development to improve accuracy and reliability, their potential lies in providing better blood glucose management and monitoring solutions for diabetic patients. Regarding tear fluid glucose detection, NovioSense has developed a miniaturized device that can be placed inside the eye to measure glucose levels in tear fluid for real-time monitoring. However, Google once attempted a similar project using smart contact lenses but abandoned it due to accuracy issues. Recent research has proposed detecting glycated albumin (GA) in tear fluid as a potential non-invasive method for monitoring blood glucose levels in diabetic patients; however, this technology is still in the exploratory stage. Additionally, DiaMonTech has developed a non-invasive device that uses infrared light to measure glucose levels in the skin.[168] The GlucoWise sensor is designed to be placed between the thumb and index finger for blood glucose measurement and is still in development, with plans to integrate machine learning for improved accuracy. NovioSense is also working on a sensor that can be placed beneath the lower eyelid to monitor blood glucose levels in tear fluid, with data wirelessly transmitted to smartphones. At the same time, Indigo is developing a single sensor that is designed to measure a large number of metabolites. The small continuous multi-metabolite monitoring (CMM) sensor is implanted just under the skin and continuously measures metabolites in the body delivering best-in-class data to aid the management of chronic diseases.[169] Biolinq[170] provides painless blood glucose monitoring through sensing technology, while One Drop[171] combines real-time blood glucose monitoring and intelligent health management to provide users with personalized recommendations. In addition, related studies such as Bai,[172] Wang[173] and Sun[174] demonstrated the potential of these technologies to improve accuracy, stability, and adaptability to physiological changes, further supporting the application prospects of non-invasive blood glucose monitoring. The development of these new technologies demonstrates significant potential for providing accurate, non-invasive, and continuous blood glucose monitoring, helping to improve diabetes management and reduce the discomfort and risks associated with traditional blood glucose monitoring methods. The tissue interstitial fluid blood glucose monitoring method based on microneedle technology uses tiny, shallow microneedles to penetrate the skin and access subcutaneous interstitial fluid for blood glucose monitoring, offering a solution for continuous and real-time monitoring without the need for fingertip blood draws. Nonetheless, the accuracy and reliability of microneedle technology still require additional research and development to ensure its effectiveness in practical applications. Commercialized glucose monitoring devices are summarized in Table 1.

Here are a few suggestions for new commercial products:

1. User experience and comfort: non-invasive devices offer the advantage of no skin punctures, reducing discomfort. New designs should prioritize comfort and ease of use, with wearable options like smart rings or contact lenses potentially appealing to younger or less frequent sensor-replacement users.

2. Accuracy and reliability: despite the appeal of non-invasive technologies, accuracy is critical. New devices must undergo rigorous clinical trials to prove reliability in varying conditions, especially for patients who use glucose data to adjust insulin.

3. Price and affordability: existing CGMs are expensive, limiting accessibility. Non-invasive devices could be more competitive with lower costs, achieved through optimized production and insurance partnerships for better pricing.

4. Personalization and intelligence: with AI and big data, future devices could offer personalized management, predicting trends and warning of blood sugar issues, enhancing user satisfaction and loyalty.

In short, for non-invasive devices to stand out, they must innovate in technology, user experience, pricing, and personalized services. As technology advances, non-invasive blood glucose monitoring has strong potential to become a key tool in diabetes management.

4. Multiplexing techniques in non-invasive glucose monitoring

Multiplexing techniques have become essential in non-invasive glucose monitoring, enabling the integration of multiple sensing modalities to achieve higher accuracy, sensitivity, and reliability. By combining different measurement principles, these approaches address the inherent limitations of single-sensor systems, such as low SNR, interference from other biological components, and sensitivity to physiological variability. We propose various multiplexing methods, including advanced combinations of spectroscopy, bioimpedance, photoplethysmography, and ultrasound, highlighting their principles, advantages, challenges, and potential for wearable applications.

Near-infrared spectroscopy + ultrasound

Near-infrared spectroscopy combined with ultrasound presents a compelling solution for glucose monitoring by optimizing both optical and acoustic measurement techniques. NIR offers non-invasive glucose estimation by measuring absorption at specific wavelengths, while ultrasound provides deep tissue penetration, improving the

Table 1 Commericialized glucose monitoring devices

Device	Principle	Measurement site	Measurement range	Target population	Operational duration	MARD value
Wizmi™[158]	NIR	Wrist skin	40–300 mg dL^{-1}	Healthy individuals	Up to 24 hours	7.23%
Tensor Tip CoG[159]	NIR	Finger skin	3.89–24.4 mmol L^{-1}	Healthy individuals & diabetics	Continuous during use	14.5–18.1%
C8 (ref. 160)	Raman spectroscopy	Waist skin	—	Healthy individuals	Not specified	—
Gluco Beam™[161]	RI	Finger ISF (interstitial fluid)	—	Healthy individuals	Up to 12 hours	—
GlucoWatch G2 (ref. 162)	RI	Wrist ISF	41–279 mg dL^{-1}	Healthy individuals	Up to 12 hours	—
Sugar Beat©[163]	RI	ISF	—	Healthy individuals	Up to 14 days	8–17%
K'Watch[175]	RI	ISF	—	Healthy individuals	Up to 7 days	—
Gluco Track[164]	Electromagnetic, ultrasound, MHC	—	4.17%–27.8 mmol L^{-1}	Healthy individuals	Continuous during use	22.7%
NovioSense[165]	Enzymatic	Tear fluid	—	Animal models	1–2 weeks	—
NIRLUS©[167]	—	—	70–300 mg dL^{-1}	Healthy individuals	Continuous during use	10.7 ± 0.5%
GWave[176]	RF	—	—	Type 2 diabetes (5 cases)	Not specified	−4.787 mg dL^{-1}
Dexcom[177]	CGM	Subcutaneous	40–400 mg dL^{-1}	Diabetics	10 days	9.0%
Abbott (Freestyle Libre)[178]	CGM	Subcutaneous	40–500 mg dL^{-1}	Diabetics	14 days	9.4%
Medtronic (Guardian Series)[179]	CGM	Subcutaneous	40–400 mg dL^{-1}	Diabetics	7 days	8.7%
Senseonics (Eversense)[180]	CGM (implantable)	Subcutaneous (implantable)	40–400 mg dL^{-1}	Diabetics	90 days	8.5%
DiaMonTech[168]	CGM	ISF	—	Healthy individuals	Continuous during use	—
GlucoWise[181]	—	Finger skin	—	—	Continuous during use	—
Indigo[169]	CGM (implantable)	ISF	—	Healthy individuals	1 years	—
Biolinq	CGM	Subcutaneous	—	Healthy individuals	—	—
One Drop	CGM	—	—	Diabetics	—	—

overall accuracy of glucose measurements. To enhance the system's SNR, researchers have developed compact quantum cascade lasers (QCLs) and tunable semiconductor lasers, narrowing the spectral width to mere nanometers. This precision reduces the influence of overlapping spectral components, which significantly improves measurement accuracy for glucose and other analytes, such as cholesterol and triglycerides. By measuring these trace components, the system can indirectly eliminate interfering variables, isolating glucose concentrations with greater reliability.

The NIR-ultrasound multiplexing approach is particularly advantageous for non-invasive applications due to its high sensitivity and tissue penetration depth, offering a robust solution for monitoring glucose in individuals with varying physiological conditions. However, as with any optical method, environmental factors and device complexity pose challenges, which are mitigated through careful device calibration and refinement of optical components.

Raman spectroscopy + bioimpedance spectroscopy

Raman spectroscopy, known for its high specificity due to unique glucose spectral peaks, can achieve precise glucose detection. With recent advances in Raman chip technology, Raman spectroscopy is now more accessible for commercial application. However, Raman-based systems often encounter stability issues under fluctuating environmental conditions, which can be addressed by combining them with bioimpedance spectroscopy (BIS).

BIS measures electrical impedance in body tissues, providing supplementary data on skin temperature and movement, which can compensate for the variability in optical measurements. By monitoring electrical impedance fluctuations, BIS captures real-time data on changes in blood volume and tissue properties that correlate with glucose levels.

The integration of Raman spectroscopy and BIS has promising applications in wearable glucose monitors, such as rings and wristbands, which could leverage both techniques to provide highly accurate, continuous, and real-time glucose readings. This multiplexed system's major advantage lies in its resilience to the physiological and environmental factors that commonly disrupt single-sensor devices. For instance, by accounting for variations in skin temperature and tissue hydration, this combined system can maintain consistent accuracy across different conditions.

Silicon photonics + photoplethysmography

Silicon photonics combined with PPG represents a low-cost and highly adaptable solution for non-invasive glucose monitoring. Silicon photonic chips emit laser light at targeted wavelengths, allowing for glucose estimation by

analyzing the returned spectra from specific subcutaneous layers. Meanwhile, PPG measures blood volume changes through light absorption, providing a secondary data source relevant to glucose fluctuations.

The real-time blood flow dynamics captured by PPG offer critical contextual information that complements glucose readings from silicon photonics. For example, while photonic measurements provide baseline glucose levels, PPG tracks pulsatile changes in blood flow associated with glucose metabolism. This dual approach not only enhances the accuracy of glucose monitoring but also allows for real-time feedback, making it suitable for wearable devices.

One of the key advantages of this multiplexed technique is its low implementation cost, as it requires only minor modifications to existing wearable platforms. This versatility makes it an ideal candidate for integration into popular consumer wearables, such as smartwatches, potentially enabling large-scale adoption. Apple Watch, for instance, has been exploring similar methods, underscoring the viability of this technique for mass-market glucose monitoring.

Multiplexing techniques significantly improve non-invasive glucose monitoring but add complexity in design, data processing, and calibration. Advanced algorithms are needed to interpret data across sensing modalities, requiring machine learning for accurate calibration in diverse conditions. Environmental factors like temperature and light sensitivity affect optical and acoustic signals, while device miniaturization and low power consumption are essential for wearable comfort. Physiological variability further complicates accuracy, despite multiplexing's complementary data benefits, and the high cost of specialized components makes balancing performance with affordability crucial for widespread adoption.

Table 2 Glucose sensing methods

Method	Category	Advantage	Disadvantage
Conventional methods	Self-monitoring of blood glucose (SMBG)	Real-time, accurate	Frequent blood sampling required, discomfort, high risk of infection
	Continuous glucose monitoring (CGM)	Continuous monitoring, early detection of glucose fluctuations	High cost, sensor replacement needed every 14 days, risk of infection and sensor malfunction due to long-term wear
	Oral glucose tolerance testing (OGTT)	Comprehensive evaluation of glucose tolerance and insulin response	Time-consuming, potential discomfort for some patients, may not capture short-term fluctuations, affected by certain health conditions
	Glycosylated hemoglobin (HbA1c) measurement	Convenient and reliable method to measure long-term blood sugar control	May not capture short-term fluctuations, affected by certain health conditions
Electrochemical methods	Sweat-based glucose sensors	Non-invasive, user-friendly, cost-effective	Less accurate than other methods, affected by factors such as sweat composition and skin temperature
	ISF-based glucose sensors	Non-invasive, provides reliable diagnostic information, accessible through simple procedures	Limited accuracy
	Tear-based glucose sensors	Non-invasive, real-time monitoring of tear glucose levels	Safety issues and power supply challenges
	Saliva-based glucose sensors	Non-invasive, easy sample collection, high sensitivity and specificity	Limited accuracy
Optical method	NIR/MIR spectroscopy	Non-invasive, fast measurement time, wide range of applications, high sensitivity and specificity	Limited accuracy in certain situations, expensive equipment required, need for calibration and validation studies
	Raman spectroscopy	High specificity, non-destructive, can detect multiple analytes simultaneously	Low sensitivity, requires specialized instruments and expertise, prone to interference from other substances
	Optical coherence tomography (OCT)	Non-invasive, high-resolution imaging, real-time monitoring, provides structural information about biological tissues	Limited penetration depth, expensive equipment, interpretation of images requires expertise
	Optical polarimetry (OP)	High sensitivity and specificity, can detect subtle changes in the polarization state of light, non-destructive measurement method	Requires specialized equipment and expertise to interpret results, limited applicability in certain environments or situations
	Fluorescence	Highly sensitive and specificity, provides visual feedback, can be used for quantitative analysis	Can be affected by environmental factors such as temperature and pH
Other methods	Millimeter-wave (mmW) and microwave (MW)	Non-invasive, high spatial resolution, suitable for monitoring physiological parameters in real-time	Limited penetration depth, susceptibility to motion artifacts, signal interference from external sources
	Ultrasound	Non-invasive, high spatial resolution, suitable for monitoring deep tissue structures	High cost, sensitive to temperature and pressure fluctuations
	Bioimpedance spectroscopy	Non-invasive, easy to use, provides information on tissue composition and hydration status	Limited accuracy and sensitivity

The future of multiplexing in glucose monitoring will focus on refining sensor integration, data processing, and wearable design. Key advancements include adaptive machine learning to identify patterns and reduce noise, minimizing the need for invasive calibrations. Biocompatible materials and flexible electronics could enable comfortable wearables like smart rings and contact lenses, transforming continuous monitoring. Integrating multiplexed sensors with mobile devices for real-time analysis could also lower costs, making these technologies more accessible. Additionally, self-calibrating systems that adapt to each user's physiology would improve accuracy and convenience for long-term use. Together, these developments will enhance the accuracy, comfort, and affordability of non-invasive glucose monitoring.

5. Conclusions

First, we summarize the above glucose detection methods in Table 2. Furthermore, non-invasive glucose monitoring technologies (e.g., optical methods, millimeter wave sensing, and ultrasound) have the advantage of not requiring blood sampling, but face significant challenges in terms of accuracy and reliability, compared to non-invasive and traditional chemical technologies. Factors such as skin pigmentation, moisture, body composition, and environmental conditions (e.g., temperature and humidity) can affect their performance, resulting in greater variability and measurement errors compared to electrochemical sensors. While electrochemical biosensors remain the gold standard in clinical applications for their high accuracy (within 5–15% RMSE), real-time monitoring, and reliability, they are invasive and require frequent calibration. Non-invasive methods hold the promise of improving patient comfort, but are currently limited by reduced accuracy, individual variability, and the need for significant advances in sensor technology, calibration algorithms, and understanding of physiological factors. Further innovation is necessary for these technologies to complement or compete with traditional methods in clinical applications. Then, in this exploration of advanced glucose monitoring technologies, we have examined the evolution and potential of multiplexing techniques in non-invasive glucose monitoring. Multiplexing, which integrates multiple sensing modalities such as NIR spectroscopy, ultrasound, Raman spectroscopy, bioimpedance, and photoplethysmography, represents a significant leap forward, enhancing measurement accuracy, sensitivity, and robustness against physiological variability. Meanwhile, integrating glucose monitoring with other biomarkers into multiplexed systems has great potential to enhance disease management, especially in conditions such as diabetes, metabolic syndrome, and other chronic diseases. Lactate is an important biomarker of metabolic activity, and monitoring lactate can provide insight into cellular oxygenation and anaerobic metabolism. Elevated lactate levels may indicate tissue hypoxia or metabolic stress, which

is particularly important in critical care settings or for patients with conditions such as sepsis or lactic acidosis. While integrating glucose monitoring with other biomarkers holds great promise, several technical challenges must be overcome to achieve accurate, reliable, and real-time measurements from multiple sensors in a single device. One of these challenges is the potential interference between different sensing targets, where glucose sensors can be affected by other molecules or substances present in the sample, resulting in inaccurate readings. To mitigate this, robust calibration methods and the use of selective sensors are required. Furthermore, multiplexed systems generate complex data from multiple sensing modalities, which requires sophisticated signal processing and data fusion algorithms to ensure accurate and meaningful information is extracted. Developing algorithms that can process and interpret data from different biomarkers in real time is a major challenge.

However, non-invasive glucose monitoring technology still has many issues that need to be addressed and solved.

About how to solve the critical problem of accuracy under fluctuating physiological conditions. It can be solved from the following aspects. **Multiplexing technology**: by combining multiple sensing modes, errors from a single sensor under complex physiological conditions can be reduced. **Machine learning and adaptive algorithms**: the machine learning models allows the system to dynamically calibrate based on individual physiological characteristics, minimizing measurement deviations caused by environmental factors like temperature and humidity. **Advancements in sensor materials**: the use of biocompatible materials and flexible electronic devices can reduce poor contact between the sensor and the skin, ensuring more stable signal transmission.

Non-invasive glucose monitoring is also affected by a variety of external factors. For example, temperature fluctuation is one of the main environmental factors that affect the accuracy of wearable sensors. Temperature changes can affect reaction rates, signal drift, and sensor sensitivity. To mitigate the effects of temperature, modern sensors are often equipped with temperature compensation. We recommend real-time monitoring of ambient temperature through a temperature sensor and dynamically adjusting the measured value through a compensation algorithm. Sweat caused by physiological factors such as exercise, weather, or stress can interfere with sensor readings, especially for electrochemical sensors. The concentration of electrolytes in sweat may change the electrochemical environment around the sensor, resulting in inaccurate readings. To address sweat interference, some wearable sensors now include sweat monitoring capabilities that allow algorithm-based compensation. Another effective strategy is to use waterproof coatings or hydrophobic materials to reduce sweat accumulation and minimize its impact on sensor performance. Food intake, especially high-glycemic index foods, can cause rapid fluctuations in blood glucose levels. These fluctuations are often reflected in the interstitial fluid, which is where many wearable glucose sensors work. We

recommend designing sensors to automatically recalibrate after meals based on the expected post-meal blood glucose curve. Using machine learning algorithms to simulate an individual's post-meal blood sugar response, combined with historical data, can improve the accuracy of post-meal measurements.

In general, non-invasive glucose monitoring technology still has great development prospects. As long as we continue to pioneer and innovate, believe there will be better development.

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

Author contributions

S. M. conducted the statistical analysis of the current development status and completed the proofreading of the manuscript. Y. H. performed the statistical analysis and review of commercial products. H. G. explored and discussed future research directions. Q. L. led conceptualization, writing and analyses. T. X. and X. Z. assisted with analyses, writing and editing.

Conflicts of interest

The authors declare no conflict of interest.

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