TOPICAL REVIEW

Optical sensors for continuous glucose monitoring

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Abstract

For decades, diabetes mellitus has been of wide concern with its high global prevalence, resulting in increasing social and financial burdens for individuals, clinical systems and governments. Continuous glucose monitoring (CGM) has become a popular alternative to the portable finger-prick glucometers available in the market for the convenience of diabetic patients. Hence, it has attracted much interest in various glucose sensing technologies to develop novel glucose sensors with better performance and longer lifetime, especially non-invasive or minimally invasive glucose sensing. Effort has also been put into finding biocompatible materials for implantable applications to achieve effective *in vivo* CGM. Here, we review the state-of-the-art researches in the field of CGM. The currently commercially available CGM technologies have been analyzed and a summary is provided of the potential types of recently researched non-invasive glucose monitors. Furthermore, the challenges and advances towards implantable applications have also been introduced and discussed, especially the novel biocompatible hydrogel aimed at minimizing the adverse impact from foreign-body response. In addition, a large variety of promising glucose-sensing technologies under research have been reviewed, from traditional electrochemical-based glucose sensors to novel optical and other electrical glucose sensors. The recent development and achievement of the reviewed glucose sensing technologies are discussed, together with the market analysis in terms of the statistical data for the newly published patents in the related field. Thus, the promising direction for future work in this field could be concluded.

1. Introduction

1.1. Clinical significance

The prevalence of diabetes has become one of the greatest concerns worldwide. It has been declared by the World Health Organization that diabetes has been estimated to be listed among the top seven causes of death over the next decade [1]. Statistical analysis for the global prevalence of diabetes is provided by the International Diabetes Federation (IDF) every year together with its projection.

The latest estimation from the IDF in 2019 is provided in table 1 below. As shown in table 1, 463 million adults throughout the world are currently suffering from diabetes and the number is expected to increase by 51% by 2045 with the current trend [2]. Considering there are approximately five billion adults worldwide, these figures mean that the global prevalence of diabetes has already reached 9.3% at present and is estimated to increase to 10.9% in 2045 [2]. Effective action is crucial for the inhibition of this global prevalence.

The high prevalence of diabetes has already resulted in severe social and financial burdens for both governments and individuals. According to the statistics, 4.2 million patients died from diabetes in 2019 and there are 231.9 adults with undiagnosed diabetes, which is over half of the current diabetic adult population [2]. Moreover, 760.3 billion USD health expenditure was spent on diabetes globally in 2019, which means an average of 1673.1 USD per diabetic patient [2]. This takes up a significant percentage of government health

Table 1. The global prevalence of diabetes in 2019 with projections [2].

	2019	2030	2045
Total world population (billion)	7.7	8.6	9.5
Adult global population (billion)[a]	5.0	5.7	6.4
Number of adults with diabetes (million)[a]	463.0	578.4	700.2
Global prevalence of diabetes	9.3%	10.2%	10.9%
Number of adults with undiagnosed diabetes (million)[a]	231.9	N/A	N/A
Number of deaths due to diabetes (million)	4.2	N/A	N/A
Total health expenditure for diabetes (billion USD)	760.3	824.7	845.0
Mean diabetes-related expenditure per patient (USD)	1673.1	N/A	N/A

[a] Note: adults refers to people between 20 and 79 years old in this case

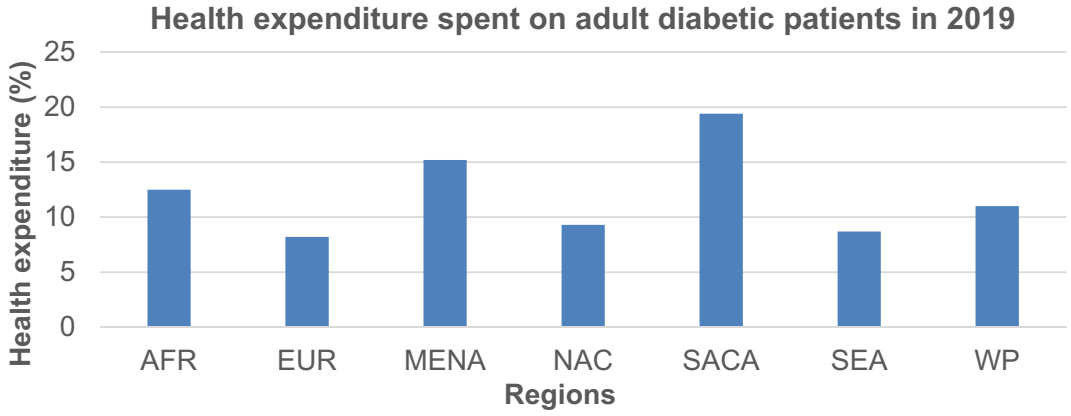

Figure 1. Diabetes-related expenditure for total health budget by regions: Africa (AFR), Europe (EUR), Middle East and North Africa (MENA), North America and the Caribbean (NAC), South and Central America (SACA), South-east Asia (SEA), Western Pacific (WP). All data were obtained from the International Diabetes Federation [2].

budgets worldwide, with 19.4% in South and Central America as the highest and 8.3% in Europe as the lowest, as shown in figure 1 [2].

Therefore, it is extremely urgent to develop a technique for the efficient diagnosis and effective treatment of diabetic patients, which would not only benefit the diabetic patients with better quality of life, but be less of a financial burden for governments.

1.2. Pathophysiology

Diabetes is a metabolic condition with patients having abnormally high blood glucose levels, resulting from either insufficient insulin production (type 1 diabetes) or severe insulin resistance (type 2 diabetes) [3]. As a hormone, insulin functions by stimulating its receptor to conduct a series of phosphorylation processes, signaling the insulin-sensitive glucose transporter four (GLUT4) to migrate from the cell cytosol to the cell surface. Hence, the glucose can be successfully transported into the cell, as shown in figure 2 [4].

This glucose-uptake response would sometimes be reduced due to perturbed signaling, so-called insulin resistance and hence the body would try to produce more insulin to compensate this deviation [4]. As a result, the blood glucose level would start rising at the point that pancreatic β cells could no longer produce sufficient insulin to maintain the balance [4]. Therefore, the blood glucose level is regarded as the basis of clinical diagnosis for diabetes. Hence, the treatment of diabetes could be achieved by either providing sufficient insulin directly from external medicine (type 1 diabetes) or enhancing the production and sensitivity of insulin within the body indirectly via non-medical treatment such as maintaining a diabetic-friendly diet (type 2 diabetes) [5].

According to the clinical statistics, the normal glucose concentration range is around 4.2–6.4 mmol l^{-1}. This range could be extended to 3.0–20.0 mmol l^{-1} for the majority of diabetic patients and hence a patient could be diagnosed if the glucose level is greater than 7.0 mmol l^{-1} [6]. For diabetic patients, the blood glucose level is supposed to be precisely monitored and carefully controlled at a normal level all the time. Hence, it is recommended that their blood glucose level be tested at least several times a day [7]. The treatment of diabetic-related hyperglycemia, which refers to an excessive blood glucose level, needs to be efficiently carried out in time and hence a frequent and accurate glucose measurement should be provided. Therefore, by continuously monitoring the blood glucose level, the effect of current treatment could be

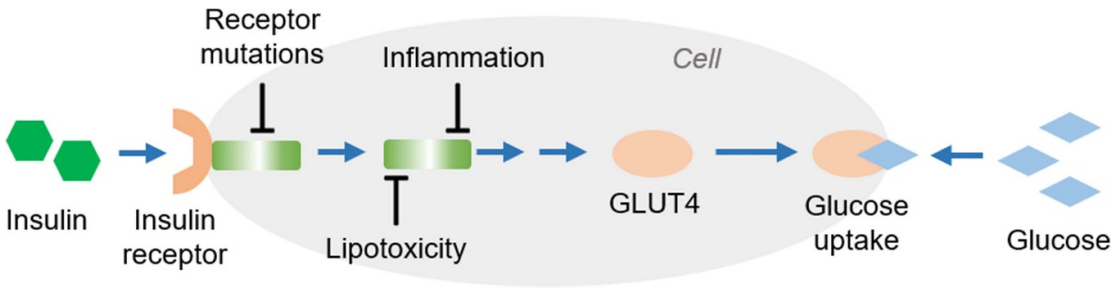

Figure 2. Glucose uptake process. Adapted from Scobie and Samaras [4].

directly evaluated and a precisely customized treatment plan could be provided to various diabetic patients according to the data gathered.

The present review will provide a general overview of the various glucose monitoring approaches available in the market and also the advanced glucose sensing technologies that have been researched recently. Multiple categories of glucose detection techniques will be introduced in the following sections and the performance of sensors is normally evaluated by certain characteristics, including selectivity, sensitivity, stability, limit of detection and response time.

2. Glucose monitoring approaches

2.1. Discrete blood sample test

As the blood glucose level is regarded as the major diagnostic criterion for diabetes, various technologies have been researched and marketed for the quick checking of the blood glucose level. Portable finger-prick blood glucometers are currently most widely applied for blood glucose monitoring, which typically measures the glucose concentration in a drop of capillary blood via the oxidation of glucose with glucose oxidase (GOx) as the catalyst [8]. The blood sample can be taken by piercing the fingertip and then loading it to a disposable test strip for chemical analysis to determine the glucose level [9].

Nevertheless, the same test is required to be performed multiple times every day with discrete data recording, which is extremely inconvenient and painful with the unavoidable frequent invasive testing to be carried out regularly even while sleeping, driving or during meetings [10]. Moreover, the blood glucose level for diabetes could significantly vary within a short time period and hence the precise dosing of insulin required for diabetes could only be achieved with a correct real-time blood glucose level. It is apparent that the limited frequency of discrete blood sample tests that could be carried out with portable finger-prick blood glucometers is insufficient for critical real-time glucose monitoring [11].

2.2. Continuous glucose monitoring

To provide convenient real-time glucose monitoring, continuous glucose monitors (CGMs) have been commercially available in the market, most of which have taken the electrochemical approach with a glucose-sensitive enzyme, while some microdialysis-based CGM systems are also available. The microdialysis-based Menarini system involves pumping a buffer solution through the biocompatible membrane catheter and hence the glucose concentration in the effluent from the catheter could be measured by applying a monitor outside the body [12]. Although this approach would be potentially more accurate, the plumbing between the microdialysis membrane and the glucose sensor introduces a considerable lag time. The major disadvantage is that the required high flowrate to minimize the lag time would lead to insufficient time to establish the glucose equilibrium between the pumped fluid and the interstitial fluid (ISF) [12]. In addition, the pump and solution bag involved make the size of the system unavoidably larger, which might result in discomfort and lower patient satisfaction [13].

For the electrochemical CGM devices available, such as Abbott, DexCom and Medtronic sensors, the enzyme-promoted electrode could be implanted under the skin and the real-time data could be wirelessly sent to a digital receiver by attaching a transmitter to the electrode [14]. Instead of taking a sample directly from capillary blood, CGM devices tend to measure the glucose concentration in the ISF for a minimally invasive outcome, as it has been proved that similar results could be obtained when the glucose level is steady [13]. Although continuous monitoring could be achieved in this way, the finger-prick tests still could not be avoided in this case to calibrate the readings of the CGM as compensation for the changing glucose level [13]. Moreover, most of the currently approved CGM devices are still short-term devices and are probably required to be replaced weekly [6].

Table 2. Comparison of currently available CGM systems [11].

CGM system (Company)	Principle	Lifetime	Accuracy	Key features	Reference
Eversense (Senseonics)	Fluorescent detection	90 d	MARD = 11.4% Calibration not required	Trend arrows Rate-of-change alerts Hyper and hypo alarms Smart device	[16]
GlucoMen (Menarini)	Microdialysis-based sensor	14 d	MARD = 10.4% Calibration required every 24 h	Trend arrows Rate-of-change alerts Hyper and hypo alarms Smart device	[17]
Navigator II (Abbott)	Enzyme-based sensor	5 d	MARD = 14.5% Calibration after 2, 10, 24, 72 h	Trend arrows Rate-of-change alerts Hyper and hypo alarms	[18]
FreeStyle Libre (Abbott)	Enzyme-based sensor	14 d	MARD = 11.4% Calibration not required	Trend arrows Smart device	[19]
G5 Mobile CGM system (Dexcom)	Enzyme-based sensor	7 d	MARD = 9% Calibration required every 12 h	Trend arrows Rate-of-change alerts Hyper and hypo alarms Smart device	[20]
G6 CGM system (Dexcom)	Enzyme-based sensor	10 d	MARD = 9.4% Calibration not required	Trend arrows Rate-of-change alerts Hyper and hypo alarms Smart device	[21]
Enlite sensor (Medtronic)	Enzyme-based sensor	6 d	MARD = 13.6% Calibration required every 12 h	Trend arrows Rate-of-change alerts Hyper and hypo alarms Insulin pumps	[22]
Guardian sensor 3 (Medtronic)	Enzyme-based sensor	7 d	MARD = 9.1% Calibration required every 12 h	Trend arrows Rate-of-change alerts Hyper and hypo alarms Insulin pumps	[23]

With improved electrochemical biosensors being widely researched, optical sensing has also drawn much attention to significantly extend the lifetime of the sensor. For example, the Eversense sensor developed by Senseonics has successfully applied the implantable optical glucose sensors into a fully implanted CGM system, which can provide real-time measurements for glucose concentration over a duration of 90 d. This product has been approved for the European market and inspired more researches focusing on optical glucose sensing, although the sensor biocompatibility and patient acceptance remain major concerns for the implantable technologies [11].

A summary of currently available commercial CGM systems is presented in table 2. The accuracy of the following systems is determined by mean absolute relative difference (MARD), which is the average of the absolute error between all values obtained from the CGM system and corresponding reference values [15]. Therefore, it could be reported in the form of percentages and a lower value of MARD would indicate higher accuracy of the device [15].

2.3. Implantable glucose monitors

As mentioned previously, implantable technologies have attracted great attention recently with the application for an implanted CGM system. An example of a theoretical closed-loop system is shown in figure 3(A) below. It involves an implanted biosensor for glucose monitoring, a control system that gives dosing instruction according to the measurement from the sensor and a drug pump that provides pharmacotherapy corresponding to the instruction [24]. In general, the smaller-sized device with a longer lifetime would be more attractive due to its convenience for implantation. However, the limitations to the extension of a lifetime for implantable devices remain key issues, including the foreign-body response, degradation and mechanical failure [24].

Apart from the well-known challenges for each type of biosensor, the major additional challenge for implanted biosensors comes from *in vivo* conditions, as the degradation of the sensor component can be accelerated by the warm and saline environment. Thus, the realization of sensor function might be impeded by the foreign-body response, as shown in figure 3(B) [26]. To be more specific, the initial degradation would start immediately on the first day of implantation due to the body's acute inflammatory response and

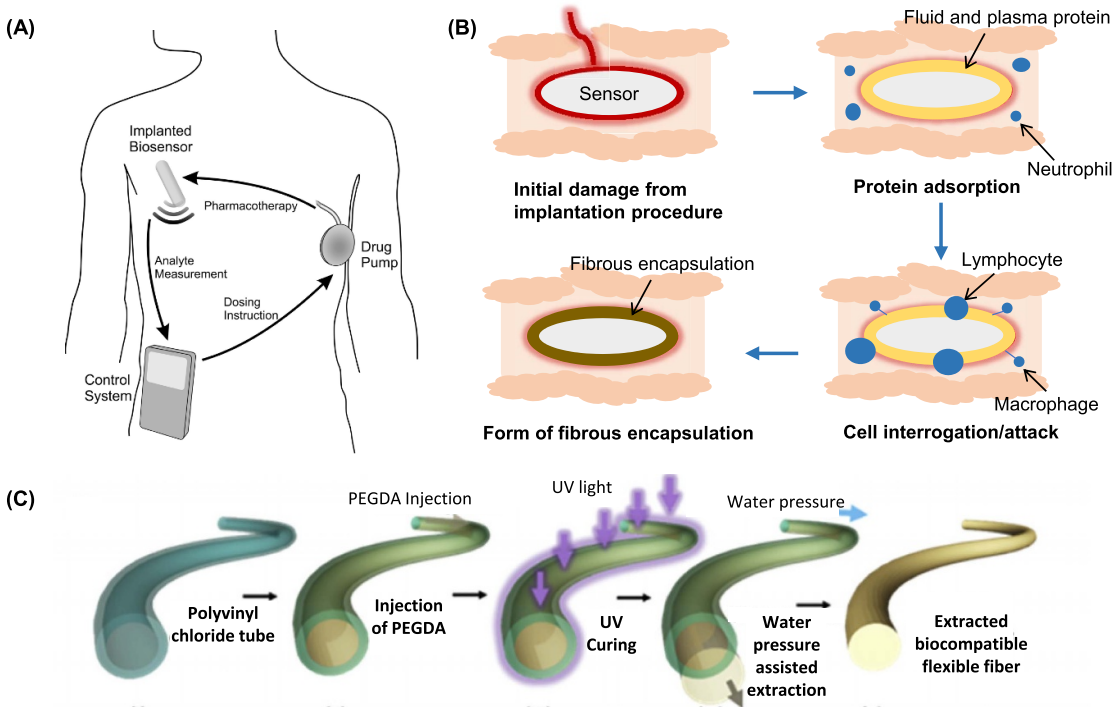

Figure 3. Schematics for an implantable biosensor. (A) Application of an implanted biosensor within the CGM system. Reprinted from [24], Copyright (2018), with permission from Elsevier. (B) Foreign-body response for the implanted sensors. Adapted from Bobrowski and Schuhmann [26]. (C) Fabrication process of biocompatible optical fibers for implantable applications. Reprinted from [25], Copyright (2019), with permission from Elsevier.

the immune system would attempt to clear the foreign body within several days. The biological compounds, especially enzyme-based compounds for detection, would degrade with a fibrotic capsule forming around the implant. The metal and electronic devices would suffer from corrosion and mechanical failure due to serious water permeation within a month, which limits the lifetime down to 1–2 weeks for the majority of the available implanted technologies [24].

To minimize the adverse effect from the implanted sensor, various researches have been carried out to fabricate the glucose-sensitive biosensor with biocompatible materials for implantable applications. For example, hydrogels have drawn much attention due to the tunability of their mechanical and optical properties [6]. Dou *et al* [27] have immobilized a boronic acid hydrogel membrane to a quartz crystal via a surface-initiated polymerization method, validating the biocompatibility of the fabricated glucose-sensitive hydrogel with microscopy. There was no evidence of cytotoxicity and inflammatory cell infiltration found within 7 d of implantation and a response time of 100 s could be achieved covering a full physiological range of blood glucose concentration, which indicated great potential for implantable applications [27].

The high performance and biocompatibility of boronic acid-functionalized hydrogel have been further proved in the form of optical fiber. Yetisen *et al* [6] have investigated the promising technology of hydrogel optical fibers as they are biocompatible and capable of incorporating functionalized analyte-sensitive compounds. The swelling and shrinking of the hydrogel matrix were observed with the variation in glucose concentration, leading to the changes in optical properties that could be easily detected, which shows the great potential of label-free optical glucose sensing for implantable applications [6]. In addition, according to Elsherif *et al* [25], a smartphone-integrated optical fiber subject to physiological conditions was fabricated for *in vivo* glucose sensing by photopolymerization, attaching the asymmetric microlens-array imprinted glucose-sensitive hydrogel to a multimode silica fiber tip, as shown in figure 3(C). The biocompatible optical fiber was found to have great potential in minimizing inflammation of the implanted site and high sensitivity of 2.6 μW mM^{-1} could be achieved with a rapid response time of 15 min and low lactate interference of approximately 0.1% [25].

To conclude, the implantable glucose sensors currently available in the market were mostly developed with enzymatic electrochemical glucose-sensing technology. Although CGM was successfully achieved with the application of these implantable sensors, they still suffer from major challenges, especially the foreign-body response. Effort has been put into materials science, aimed at minimizing the adverse impact from the foreign-body response. Hence, much attention has been paid to the biocompatibility of materials

when fabricating a novel glucose sensor. The hydrogel matrices have been found to be highly biocompatible recently. Hence, boronic acid-functionalized hydrogel optical fibers have been fabricated and characterized, achieving both high sensitivity and high biocompatibility, which shows great potential for future implantable applications. However, a large number of *in vivo* tests are still required to be carried out for further validation.

2.4. Non-invasive glucose monitoring

Although currently available CGM systems can provide real-time glucose measurements continuously with a feedback loop of insulin pumps for efficient glucose monitoring, they are still of low patient compliance due to the short lifetime and necessity of calibrations [6]. To achieve more user-friendly glucose monitors, non-invasive glucose monitors in the form of wearable devices have attracted much attention recently. The sensors applied for the currently developed non-invasive monitors are mostly electrochemical or colorimetric. The electrochemical sensors could easily achieve continuous monitoring by transmitting the real-time data to wireless electronics, while colorimetric sensors could be directly read by the naked eye without the aid of additional equipment [28].

The most well-researched non-invasive glucose monitoring technology is epidermal electrochemical monitoring, whose commercialized applications have already been approved and is currently available in the market. Instead of directly measuring the blood glucose level, this type of glucose monitor obtains real-time glucose concentration via biofluids such as skin ISF or sweat. As shown in figure 4(A), glucose in blood vessels would diffuse via the endothelium or sweat glands and hence there would be a correlation between the glucose concentration in these biofluids and the blood glucose level [29].

The first commercially available non-invasive glucometer, GlucoWatch, is wearable around the wrist with an enzyme-based electrochemical sensor, as shown in figure 4(B), which measures the glucose concentration of ISF rather than the real blood glucose level [29]. This technology involves the application of reverse iontophoresis, where an ignorable current would be applied to the skin resulting in the ion transfer [31]. As sodium ions are the major charge carriers at neutral pH, the migration of the sodium ions would result in an electro-osmotic flow of the ISF from the skin to the cathode. Hence, the glucose is transported to the cathode with this flow [31]. At the cathode, there is a standard glucose sensor measuring the glucose concentration directly by the enzymatic method, i.e. oxidization by an enzyme, such as GOx. It is one of the most investigated methods for glucose monitoring since having access to a sample of glucose means it has a high level of accuracy.

However, rapid changes in glucose concentration could hardly be detected accurately for real-time glucose monitoring via GlucoWatch. Moreover, skin irritation from the applied current becomes one of the most considerable adverse impacts, resulting in low patient satisfaction [29]. Therefore, the concept of tattoo-based glucose monitoring has been applied to overcome this limitation by reducing the current required. As shown in figure 4(C), Bandodkar *et al* [31] have applied the same reverse iontophoresis electrochemical sensors onto a temporary-tattoo platform, monitoring the sweat electrolytes and metabolites with a lower-voltage glucose-oxidase-modified Prussian Blue transducer. This provides a flexible, low-cost and body-compliant platform for non-invasive ISF glucose monitoring [29].

In addition to ISF, glucose sensing via other biofluids has also been widely researched. Sweat is one of the most attractive bio-fluids for non-invasive applications as it is able to be collected directly from outside the body, which would make this continuous process more convenient and comfortable for the patients [29]. This idea has been converted into various wearable patch-based glucose monitors. As shown in figure 4(D), an ultrathin and stretchable patch has been designed with conformal skin contact and high performance under physical deformation, where gold-doped graphene has been introduced to improve the electrochemical activity towards high glucose monitoring sensitivity [32]. To minimize interference from environmental conditions, pH and humidity sensors have been integrated with the glucose sensor for continuous calibration [29].

Similar to sweat, the tear is another kind of bio-fluid that can be directly collected from outside the body, which has attracted various research in contact lens or eyeglasses-based detectors. Yao *et al* [33] have presented a wireless and continuous glucose monitor in contact lens form with an integrated enzyme-based electrochemical glucose sensor and telecommunication circuit. As shown in figure 4(E), the wireless data transmission results for the integrated contact lens glucose sensor could be characterized via the corresponding wireless test setup. The sensor was characterized and tested with a polydimethylsiloxane eye model and mimicked tear fluid, which indicated great potential for future application in non-invasive glucose monitoring [33]. However, further investigations are required in terms of protein fouling and stability decaying with time and temperature, the limited operational range for *in vivo* testing and the gas permeability of the polymer substrates for the comfort of patients [33].

In addition, a wearable eyeglasses-based non-invasive tear-sensing system has been developed more recently for multiple analytes including glucose, as shown in figure 4(F). Here, an on-line fluidic device has

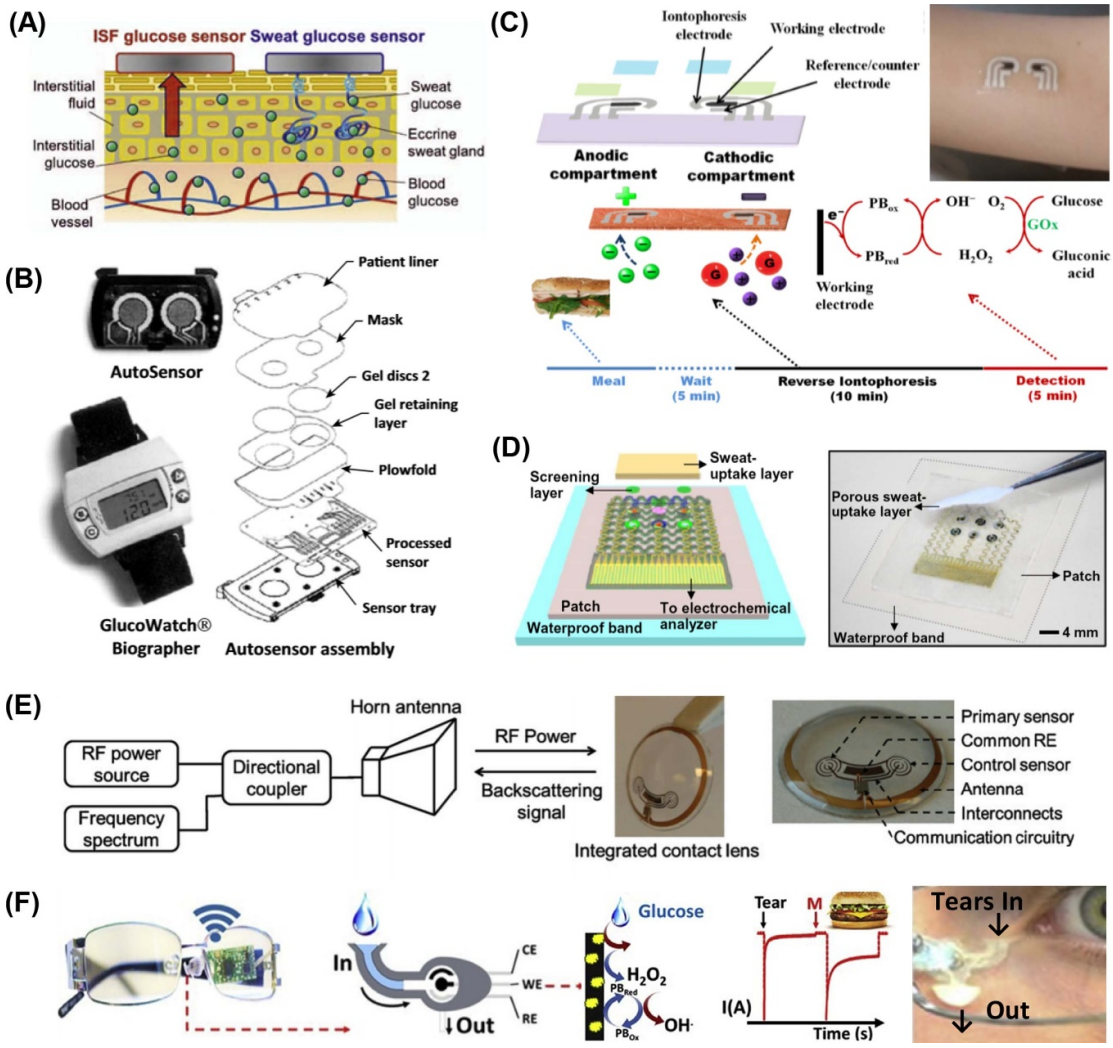

Figure 4. Non-invasive glucose monitors. (A) Schematic diagram for biofluid sensing. Reprinted from [29], Copyright (2018), with permission from Elsevier. (B) GlucoWatch electrochemical glucometer, sensing ISF. Reprinted from [30], Copyright (2014), with permission from Elsevier. (C) Temporary tattoo-based glucose monitor, sensing ISF. Reprinted with permission from [31]. Copyright (2015) American Chemical Society. (D) Wearable patch-based glucose monitor, sensing sweat [32]. Copyright (2017) American Association for the Advancement of Science. (E) Integrated contact lens glucose sensor, sensing tears. Reproduced from [33]. © IOP Publishing Ltd. All rights reserved. (F) Eyeglasses-based glucose monitor, sensing tears. Reprinted from [34], Copyright (2019), with permission from Elsevier.

been mounted onto the eyeglasses nose-bridge pad to allow the direct collection of stimulated tears [34]. To avoid some of the drawbacks of sensors based on the contact lens, including limited user compliance and potential vision impairment due to the embedded sensor system, the electrochemical detection system of this eyeglasses platform is designed to be placed outside the eye area, collecting stimulated tears on the external miniaturized flow detector with a wireless electronic backbone integrated into the eyeglasses frame [34].

Another promising bio-fluid is respiratory fluid and the critical biomarkers for glucose analysis could be collected non-invasively and continuously in the form of either volatile organic compounds from exhaled gas or exhaled breath condensate [35]. It has been reported that for a healthy person, the glucose concentration in respiratory fluid is only around 0.4 mmol l^{-1}, which is more than tenfold lower than the blood glucose level. Such a high concentration gradient could lead to rapid glucose transport and equilibrium between the respiratory fluid and plasma and hence a glucose monitor with less lag-time could potentially be developed. Nevertheless, the sensitivity and resolution of currently available glucose sensors should be largely improved due to the low glucose concentration in respiratory fluid, which has become the major challenge for further development of glucose monitors via exhaled breath [35].

To conclude, various researches for non-invasive CGM have been carried out focusing on glucose-sensing methods via bio-fluids, including ISF, sweat or tears, as summarized in table 3 below. In addition, respiratory fluid is also considered promising for non-invasive glucose monitoring, although numerous researches should be carried out for developing a glucose sensor with higher sensitivity and resolution. It has been

Table 3. Non-invasive glucose monitoring.

Platform	Sampling	Advantages	Challenges	Reference
GlucoWatch	ISF (reverse iontophoresis)	• Combined electronics for measurement and data storage • Portable	• Skin irritation • Expensive	[29]
Temporary tattoo	ISF (reverse iontophoresis)	• Cost effective • Flexible • Body compliant	• Lag time • Inconsistent ISF extraction efficiency • Interference from sweat	[31]
Wearable patch	Sweat (exercise)	• Controlled sweat uptake • Calibration with pH/temperature	• Lag time • Large data required for correlation	[32]
Contact lens	Tears (natural secretion)	• Easily accessible • Wearable for a long time • Continuously sampling	• Limited user compliance • Potential vision impairment • Protein fouling • Stability decaying	[33]
Eyeglasses	Tears (stimulation)	• Integrated wireless electronics • Does not affect vision	• Inconvenient sampling	[34]

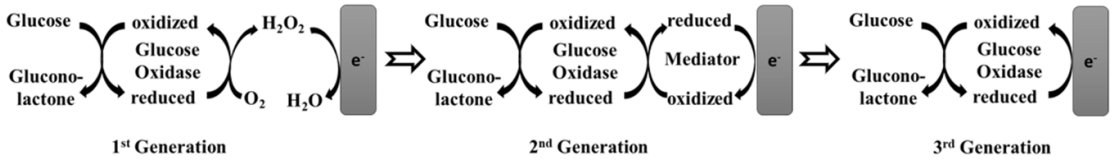

Figure 5. Schematic diagram for the principle of first, second and third generation of enzymatic glucose sensing.

demonstrated that the glucose concentration in bio-fluids is correlated with blood glucose concentration and hence non-invasive glucose monitoring could be achieved with acceptable accuracy. However, there are still considerable challenges to overcome, especially the concerns that the data taken from the bio-fluids would result in a lag behind the actual real-time blood glucose level. In addition, the inconsistency of ISF extraction efficiency might significantly affect the accuracy and other types of bio-fluids might also interfere with the result, thus deviating from the designed correlation. This means that numerous studies are strictly required to check the accuracy and reliability of these sensing systems.

3. Electrochemical glucose sensors

3.1. Enzyme-immobilized electrodes

The most traditionally researched type of glucose sensors is the enzyme-based electrochemical sensor [36]. This kind of biosensor was researched based on the theory of immobilizing GOx on an electrode, which was first proposed in the 1960s [15].

For the first generation of enzymatic glucose sensors, the oxidation of glucose takes place in the presence of GOx, oxygen and water to form gluconic acid and hydrogen peroxide. The glucose could immediately react with oxygen at the electrode with the catalytic enzyme and hence the glucose concentration could be determined by detecting the amount of either the oxygen consumed or the oxidation product generated [28]. However, there is concern that the sensor would be significantly affected by the environment of the blood sample, as sufficient oxygen is required for the reaction as the mediator and the interference of the electroactive species is unavoidable [7].

In the second generation of enzymatic glucose sensors, the concept of an artificial mediator has been developed to provide an electron acceptor for the replacement of oxygen and the direct electron transfer to the electrode has been achieved in the third generation of enzymatic glucose sensors, as shown in figure 5 below. Nevertheless, it still faces problems with inefficient electron transfer due to the presence of a thick

protein layer and the adverse impact from pH, temperature and humidity within the body environment on enzyme activity is another considerable issue [37].

3.2. Non-enzymatic electrodes

To eliminate the interference that resulted from the inhibition of enzyme activity and electron transfer, various enzyme-free approaches have been widely investigated recently. For example, a variety of metal-based electrodes have been researched as alternative catalysts for the replacement of the enzyme [38]. In this case, the glucose is supposed to be adsorbed onto the electrode for direct oxidation on the material surface and hence this process has significantly relied on the available site area, which would lead to a short lifetime of this type of glucose sensor [7].

Instead of studying a pure metal electrode, researchers paid more attention to various metal-composite-based materials, as they could potentially take advantage of all their components [29]. They are normally fabricated with a layer of nano-structured material coated on the bulk substrate of another material [39]. In addition, it has also been established that the electrochemical biosensors could potentially be coated with a micro-layer of polymer because of its outstanding selectivity [7]. For example, hierarchical platinum micro- or nano-structured coatings have also been developed for non-enzymatic glucose-sensing electrodes, improving the sensitivity, selectivity and stability with a novel measurement scheme (Unmussig *et al* [40]). Unmussig *et al* (2018) have applied the technique of both electrochemical deposition and colloidal synthesis to fabricate a hierarchical structure with high surface roughness. Hence, the sensitivity could reach 473 μA cm^{-2} mM^{-1}, which shows a ten-thousandfold increase in the sensitivity compared to that of the normal electrode. This study shows promising results for the hierarchical platinum nanostructured electrodes to be considered as a potential candidate for next-generation continuous glucose monitors.

As nanotechnology has become one of the hottest research topics recently, graphene or nanosheet-based electrochemical sensors with their better electrocatalytic activity have attracted wide interest from researchers [41]. The nanostructures would usually result in large surface area, high conductivity and low interference to the electrochemical reaction [7]. It has also been established that metal-free chemical vapor deposition graphene film could potentially be applied as a substitute for metal-based coatings to avoid the interference from transfer residue [42].

In general, higher sensitivities and lower detection limits could be achieved with carbon nanomaterial-based electrochemical glucose-sensing electrodes compared to traditional electrodes [37]. To be more specific, carbon nanotubes (CNTs) could capture and promote the electron transfer from analytes more efficiently due to their 1D hollow tubular nano-chemistry, leading to quicker response time and higher sensitivity [37]. For graphene, it has been found that the delocalized π bonds above and below the basal plane would contribute to the high electrical conductivities and mobilities within the plane and hence faster electron transfer could be achieved [37]. By applying carbon nanomaterials for CGM, the issues related to transition metals could be avoided and hence the electrodes would be potentially more biocompatible than traditional electrodes.

The performance of researched glucose-sensitive electrodes based on CNT or graphene are summarized in table 4 below, involving both enzymatic and non-enzymatic electrochemical electrodes. It was found that non-enzymatic electrodes could generally achieve a much lower detection limit than the enzymatic electrodes. However, some drawbacks of electrochemical sensors could not be simply overcome by the more advanced materials substituted. For instance, the readings from electrochemical sensors could unavoidably be influenced by the electromagnetic fields within the patients' bodies [36]. Moreover, it has a limited lifetime and frequent replacement is required every week [6]. Hence, alternative glucose-sensing methods have recently been considered, which will be discussed in the following sections.

4. Optical glucose sensors

4.1. Glucose recognition substrates

4.1.1. Glucose oxidase

As discussed in the previous section, most electrochemical sensors could achieve selective recognition of glucose by measuring the oxidase consumed or the oxidation product generated in the electrochemical reaction between the electrodes and glucose. Without the presence of electrodes and the electrochemical process, alternative glucose recognition methods should be applied for the optical glucose sensors.

Typical enzymes such as GOx could also be applied with optical glucose-sensing technologies, especially fluorescent sensing. One of the working principles is that the enzymes or coenzymes would change their optical properties when binding with glucose. For example, the intensity of the intrinsic fluorescence for the protein within the enzyme would shift upon binding with glucose, while the absorption spectra remain unchanged [50].

Table 4. Summary for the performance of CNT/graphene modified electrodes.

Category	Electrode	Detection range (mM)	Detection limit (μM)	Sensitivity (μA mM^{-1} cm^{-2})	Reference
Enzymatic	Pd-GOD-nafion CNT	<12	150	N/A	[43]
Enzymatic	CNT nanoelectrode arrays	2–30	80	N/A	[44]
Enzymatic	GOD-graphene-chitosan	0.1–10	10 ± 2	110 ± 3	[45]
Enzymatic	Graphene-CdS	2–16	700	N/A	[46]
Enzymatic	CNT fiber	2–30	25	N/A	[47]
Non-enzymatic	CNT/Ni	0.005–7	2	1433	[37]
Non-enzymatic	CuO-MWCNTs	<1.2	0.2	2596	[48]
Non-enzymatic	GO-thionine-Au	0.2–13.4	0.05	N/A	[49]

Another working principle is to measure the consumption or generation of metabolites caused by GOx, including the oxygen consumed, the hydrogen peroxide generated or the acid produced within the reaction [50]. These kinds of sensors are kinetic by nature, but a reagent is normally required to be consumed, which is a non-reversible process resulting in a limited lifetime [50]. Therefore, researchers have been putting increasing effort into alternative glucose recognition methods with a reversible process in order to extend the lifetime for the next-generation sensors.

4.1.2. Concanavalin A

The plant lectin concanavalin A (ConA) is considered as one of the commonly applied functional compounds for glucose recognition due to the affinity between these two molecules [50]. The ConA tetramer involves two dimers with four sites for the binding of glucose, which could also agglutinate biologically relevant complexes including glycoproteins, starches and erythrocytes [50]. Therefore, sensors could be designed as competitive assays based on the competitive binding of glucose and a labeled carbohydrate, including dextran or a glycated protein [50]. This principle is most widely applied with fluorescent sensors, as the protein and the competitor could all be labeled with distinguishing fluorescent dyes. However, this type of sensor would suffer from low stability as the unbound lectin would tend to be aggregated irreversibly within several hours, which would adversely affect the glucose-sensing ability [50].

In addition, ConA could also be applied in glucose sensing based on surface plasmon resonance (SPR), as the competitive binding of glucose would lead to a variation in plasmonic absorbance and wavelength correlated to glucose concentration [50]. It is considered as a promising candidate for implementation in non-invasive glucose monitoring, which could be further optimized by improving its particle stability and correlating the effect of pH values [50].

4.1.3. Boronic acids

Boronic acids have been found to be a competitive alternative as a glucose recognition agent, since they are capable of acting as molecular receptors for saccharides, including glucose [50]. Most of the optical sensors currently under research are fabricated from the polymerization of glucose-sensitive compounds, especially boronic acid and its derivatives, which measure the glucose level via the equilibrium principle, as shown in figure 6 below.

To be more specific, boronic acids are able to interact with glucose reversibly in aqueous solution, forming ring cyclic esters [50]. Moreover, the geometry of boronic acids could change with the variation of pH values according to its relationship between pKa values. The original state of boronic acids is uncharged and trigonal at low pH values (pH < pKa), while this could turn into a negatively charged tetrahedral form with the presence of hydroxyl ion, which is more stable at higher pH values (pH > pKa) and can bind with glucose more easily [51].

Hence, compared with the electrochemical sensors measuring glucose consumption, boronic-acid-based optical sensors could eliminate the requirement for the presence of a mediator, which is more likely to significantly reduce the lag time of readings [36]. Besides, although pH and other environmental parameters could considerably interfere with the reaction between boronic acid and glucose , the problem could be controlled by the selection of the most appropriate boronic acid derivatives [36].

In addition, boronic acid and its derivatives have been recently applied in fabricating biocompatible glucose-sensitive hydrogel for implantable applications, as discussed in section 2.3. As previously mentioned in section 2.2, the MARD is an effective way to statistically evaluate the performance of glucose sensors. Implantable boronic-acid-based optical sensors have been recently researched whose MARD could achieve as

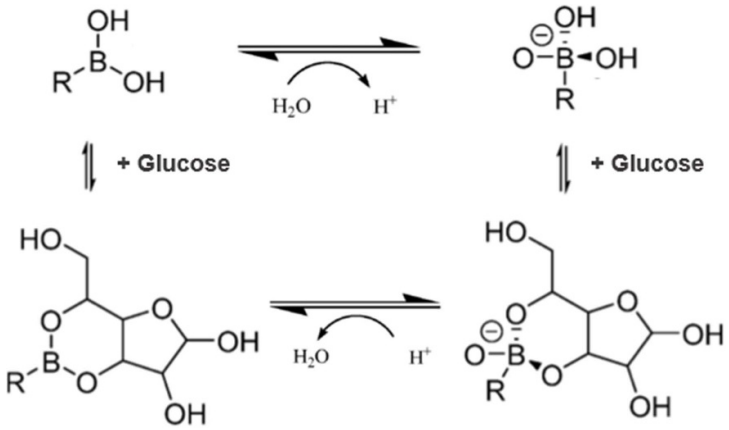

Figure 6. Schematic diagram of the equilibrium in glucose and boronic acid derivatives.

low as 10%, although only 60% of the sensors produced proved to have such a low MARD [52]. Hence, boronic-acid-based optical sensors are considered as one of the most prospective candidates for *in vivo* CGM.

4.2. Fluorescence

The application of the fluorescent technique for optical glucose sensing has been widely researched. In this approach, glucose binds to glucose-sensitive compounds such as ConA or boronic acid derivatives, together with another molecule labeled with a fluorophore. Hence, the fluorescence could emit various intensities according to the glucose concentration [28]. To be more specific, the most widely applied principle behind the fluorescent technique is fluorescence resonant energy transfer (FRET). The donor is usually the fluorophore, which is the key molecule that emits fluorescent light, while the acceptor is usually the receptor, which is a substance that can efficiently bind to glucose, such as enzymes, boronic acid derivatives, glucose binding proteins or quantum dots [53]. As shown in figure 7(A), glucose and fluorophore are in a competitive relationship for successfully binding with receptor sites. With a higher concentration of glucose, the glucose would bind more easily to the receptor. Therefore, the acceptor-donor link between the fluorophore and receptor would be broken with the presence of glucose [53]. As a result, the electron sharing would be reduced and hence the fluorescence could be increased and vice versa [53].

ConA was applied as the glucose recognition compound in the majority of fluorescent glucose-sensing assays researched. Aloraefy *et al* [56] have investigated a minimally invasive FRET-based glucose biosensor *in vitro*, whose high effectiveness has been proved with an energy transfer efficiency of 0.98 in 400 mg dl^{-1} glucose. It was demonstrated that the sensor could achieve a MARD below 11% with a detection limit of 25 mg dl^{-1} and an average response time of 15 min [56]. However, the stability of the sensor has become a major concern as the fluorescence response would significantly decay over 72% within 30 d [56].

As shown in figure 7(B), Locke *et al* [54] have developed a layer-by-layer coating for the hydrogel membrane cavity to achieve FRET-based glucose sensing, where the competitive binding principle has been applied with ConA as the functional layer. This sensor was expected to be implanted under the skin. Hence, the superhydrophobic hydrogel was applied for less biofouling and longer lifetime [54]. The fabricated hydrogel membranes coated with 5, 10, 15, 30 and 40 bilayers have been characterized and compared, among which the leaching has found to be considerably reduced with 30 bilayer coating [54].

Boronic acid and its derivatives have drawn much attention as an alternative to ConA. Freeman *et al* [58] have evaluated the FRET-based CdSe-ZnS quantum dots with boronic acid as the functional glucose recognition compound and it was found that the detection limit achieved could be as low as 1.8 mg dl^{-1}. In addition, Shibata *et al* [55] have introduced the concept of injectable FRET-based hydrogel microbeads, as shown in figure 7(C). The fluorescent monomers with glucose-sensitive sites have been synthesized with sufficient intensity for *in vivo* glucose monitoring, which could be achieved by simply injecting the microbeads under the skin via a needle [55]. The fabricated microbeads have been tested with an injection into a mouse ear and the glucose-sensing process has proved to be highly sensitive and completely reversible [55].

The key characteristics of these researched sensors mentioned above are summarized in table 5 below. In general, fluorescence glucose sensors are considered to be promising as they have significantly high glucose sensitivity even at considerably low glucose concentrations [57]. Besides, specific molecules have unique

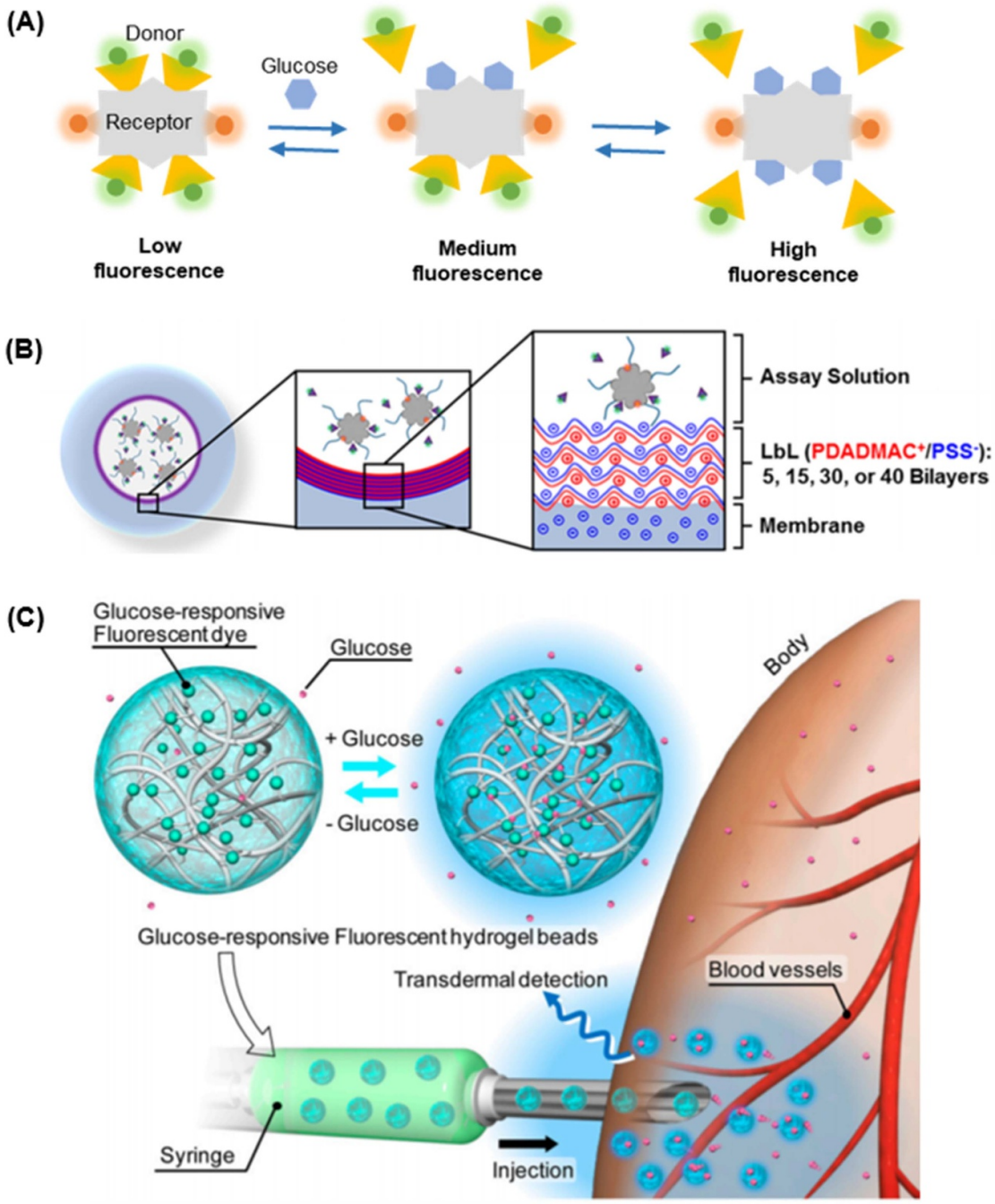

Figure 7. Schematic diagrams for the principle and application of FRET. (A) Principle of FRET. Adapted from Locke *et al* [54]. (B) Application of the layer-by-layer coating to the membrane cavity wall. Reprinted with permission from [54]. Copyright (2018) American Chemical Society. (C) Application of injectable fluorescence-based hydrogel microbeads for CGM [55]. Copyright 2010 Proceedings of the National Academy of Sciences of the United States of America.

optical properties, which could lead to high specificity [57]. Moreover, the recalibration for local tissue reactions is not frequently required [57]. However, the unavoidable photobleaching and scattering would negatively affect the readings for *in vivo* glucose monitoring [6]. In addition, sensitivity to the local environment condition, such as pH, might affect the dye response as well [57]. The potential toxicity of implanted dyes is another critical concern that cannot be ignored [57].

4.3. Spectroscopy

4.3.1. Infrared spectroscopy

Optical absorption spectroscopy is another promising optical approach for quantitative glucose sensing. In general, spectroscopic techniques detect the presence of substances by measuring the amount of light being absorbed, passed through or given off by the substance, which is termed absorbance, transmittance and

Table 5. Examples of fluorescent glucose sensors under research.

	FRET-based glucose biosensor	Layer-by-layer coated hydrogel membrane	Fluorophore-labeled CdSe quantum dots	Fluorescence-based hydrogel microbeads
Functional compound	ConA	ConA	Boronic acid	Boronic acid
Testing environment	In vitro	Solution	Solution	In vivo
MARD (%)	<11	11 ± 0.9	N/A	N/A
Detection range (mg dl^{-1})	<400	50–600	18–270	62.5–500
Detection limit (mg dl^{-1})	25	N/A	1.8	N/A
Response time (min)	15	15	N/A	N/A
References	[56]	[54]	[58]	[55]

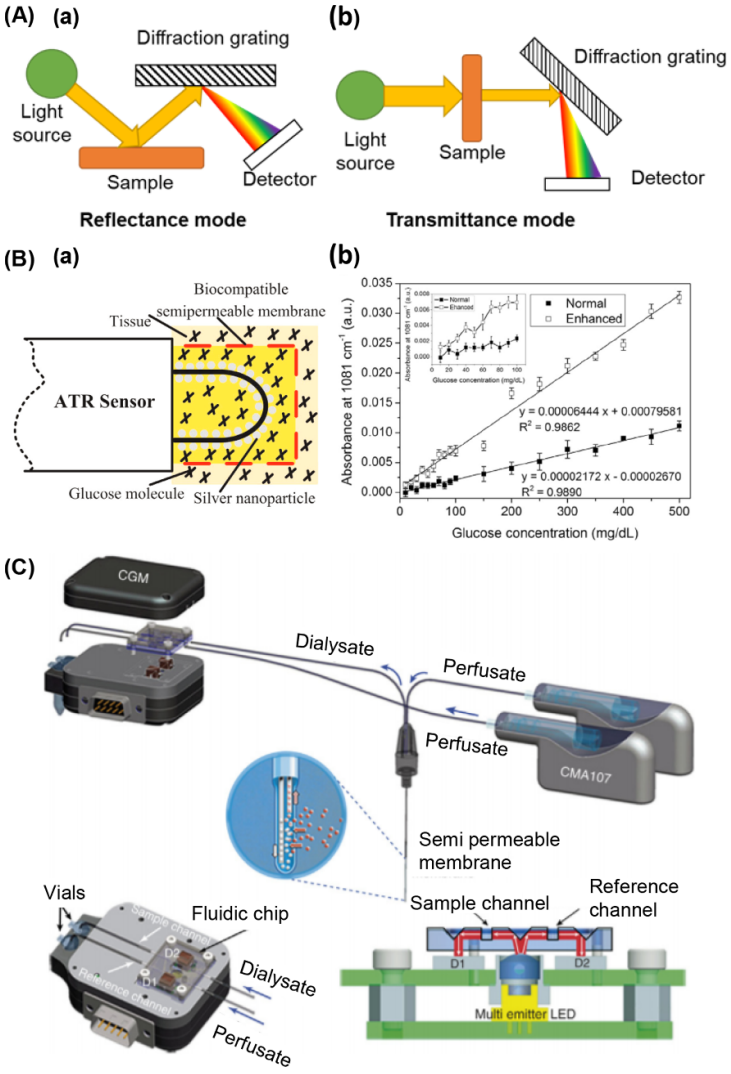

Figure 8. Schematic diagrams for glucose sensing via infrared spectroscopy. (A) Basic principle of infrared absorption spectroscopy with (a) reflectance mode and (b) transmittance mode. Adapted from Gonzales *et al* (2019). (B) Implantable silver-nanoparticle-modified fiber-optic attenuated total reflection (ATR) sensor with (a) schematic illustration and (b) performance plot of the spectra. Reprinted from [60], Copyright (2015), with permission from Elsevier. (C) *In vivo* chip-based near-infrared (NIR)-CGM sensor with microdialysis catheter and pumps. Reprinted from [61], Copyright (2014), with permission from Elsevier.

emission, respectively [53]. In the case of glucose sensing, considering the tissues of the body are too thick for transmission measurements at the wavelengths required, the reflectance is measured alternatively. This refers to the phenomenon that when directing the light at the surface of the tissue, the light would travel some distance into the skin and a small percentage would re-emerge close to the site [59]. The schematic illustration for the basic principle of infrared spectroscopy is shown in figure 8(A) below.

Table 6. Examples of glucose sensors based on Raman spectroscopy under research.

	GOx-modified AgNP-based SERS probe	Au-modified glucose sensor for SERS	AgNP-modified graphene oxide for SERS
Function layer	GOx	Boronic acid	Boronic acid
Detection range (mg dl^{-1})	36–252	18–180	36–360
Detection limit (mg dl^{-1})	0.02	N/A	N/A
References	[63]	[64]	[65]

The studies have been mostly focused on mid-infrared (MIR) and NIR range for potential implantable applications. Li *et al* [60] have presented an implantable fiber-optic glucose sensor based on MIR ATR spectroscopy, as shown in figure 8(B), which was fabricated in a U-shape structure to achieve longer effective optical length within the limited space for implantable applications and hence improve its sensitivity to glucose. Moreover, the sensor was modified by silver nanoparticles with covalent bonding, whose sensitivity and resolution were proved to be around three times greater than conventional sensors [60]. Besides, Mohammadi *et al* [61] have investigated a chip-based NIR sensor with its application in CGM systems, as shown in figure 8(C). The linear calibration curve was obtained via *in vitro* measurements for glucose concentrations in the range of 0–400 mg dl^{-1}, followed by *in vivo* measurements with the NIR-CGM system, which showed that the detection limit was about 20 mg dl^{-1} and an average MARD of 13.8% could be achieved [61].

To conclude, in the MIR region, the absorption bands result from the stretching and bending of the molecules. Hence, one of the major problems is the significant interference from the background adsorption bands [62]. On the other hand, it is the overtone vibrations that result in the absorption bands in the NIR region. Hence, it has been proved that minimal water absorption bands could be achieved with a clear glucose peak within this region [62]. In addition, it has been shown that approximately 90%–95% of the light from NIR spectroscopy penetrates through human skin, which proves that the NIR approach is effective and less harmful to the tissue [28].

However, the strong spectral similarities between glucose and other sugar components within the tissue remains a considerable challenge for this technique, and the complicated scattering of the tissue also increases the difficulty of measurement [53]. In addition, water background absorption and variation in the location on the skin between measurements easily interferes with the spectrum [59]. Therefore, some other spectroscopy technologies were also investigated for glucose readouts to overcome these drawbacks, including Raman spectroscopy, which could provide well-defined absorption peaks without inference from water, as will be discussed in the following section.

4.3.2. Raman spectroscopy

Raman spectroscopy has also been considered as one of the most promising approaches for glucose sensing. The Raman scattered light could be captured and filtered to be sensed by the detector, transmitting signals for the computer to process with a corresponding Raman shift. Similar to the infrared absorption approach, specific bands could be obtained with Raman spectroscopy according to the concentration, while the overtone bands are weaker in this case [62]. Hence, compared to the NIR approach, the target peaks could be more easily identified with Raman, while it would take a longer time to obtain the spectrum [28]. Due to practical considerations, surface-enhanced Raman scattering (SERS) has become the most widely applied technique for its enhanced Raman signal response with higher sensitivity, while the low surface adsorption ability of glucose remaines a critical challenge [63].

A considerable number of studies have been carried out, with the aimof improving the sensitivity and selectivity to glucose via modified Raman-active substrate, as summarized in table 6. For example, Qi *et al* [63] developed a glucose-sensing chip fabricated by the electrostatic assembly of GOx over silver-nanoparticle-functionalized SERS substrate, which could achieve high sensitivity with a detection range of 36–252 mg dl^{-1}, covering the full range of human blood glucose level. Besides, Sharma *et al* [64] have investigated a gold-film-modified nanosphere substrate with bisboronic acid receptors for glucose recognition, showing considerable potential for *in vivo* glucose monitoring with a detection range of 18–180 mg dl^{-1}. In addition, Pham *et al* [65] have also presented a novel SERS substrate, self-assembling 4-mercaptophenyl boronic acid (4-MPBA) on the surface of a silica-coated graphene oxide modified with silver nanoparticles, which could achieve a detection range of 36–360 mg dl^{-1}. All of these studies have shown the possibility of further application in CGM.

Nevertheless, most researches in this field are still at the stage of characterizing the novel sensor with laboratory solution. Therefore, a large number of further investigations are required to be carried out, focusing on *in vivo* tests towards the final applications on non-invasive glucose monitoring in the future.

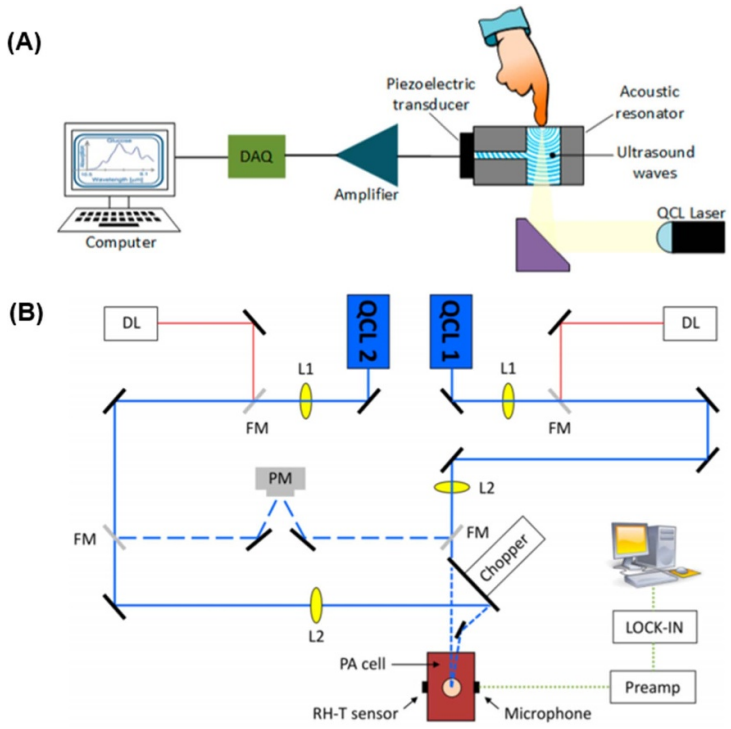

Figure 9. Schematic diagrams for photoacoustic spectroscopy. (A) Basic single-QCL setup. Reproduced from [53]. CC BY 4.0. © 2019 by the authors; licensee MDPI, Basel, Switzerland. (B) Novel dual-QCL setup. Reproduced from [66]. CC BY 4.0. © 2016 by the authors; licensee MDPI, Basel, Switzerland.

4.3.3. Photoacoustic spectroscopy

Photoacoustic spectroscopy has been considered as another candidate for promising non-invasive blood glucose monitoring technologies. This technology employs short laser pulses with a wavelength that is absorbed by a specific molecule in the fluid to produce microscopic localized heating, dependent on the specific heat capacity of the tissue. As shown in figure 9(A), the basic setup includes a quantum cascade laser (QCL), where the light is emitted and then impacts the sample, generating the ultrasound wave. The wave propagates through the acoustic resonator to the detector, where the electrical signal could then be amplified, digitized and sent to the computer [53].

A modified setup has been studied by Kottmann *et al* [66] with two QCL sources, as shown in figure 9(B), improving the sensitivity for the *in vivo* detection of glucose by setting one wavelength covering the strong glucose absorption while the other is only covering the background wavelengths. Although the potential of applying photoacoustic spectroscopy into non-invasive CGM systems has been revealed and proved, few projects have been undertaken recently on this concept with a novel CGM system. Hence, a large number of investigations should be undertaken for the clinical validation.

4.4. Surface plasmon resonance

SPR describes the resonant oscillation of conduction electrons that occur due to the radiated electromagnetic field when light hits a metal film at the interface of media with different refractive indices, with the resultant electromagnetic waves called surface plasmon polaritons [53]. As shown in figure 10(A), the laser source radiates polarized monochromatic light through a prism and the electromagnetic field could be produced by the plasma oscillations of the free electrons at certain resonant angles, resulting in a significant reduction in the power of the reflected light [53]. As the evanescent electric field is highly sensitive to changes in the refractive index of the medium, the SPR resonance peak could be detected with various resonant frequencies resulting from the variation of refractive index corresponding to the change in glucose concentration [53].

As shown in figure 10(B), Zheng *et al* [67] have recently developed a reflective SPR optical fiber with GOx immobilized as the glucose-recognizing film, whose refractive index could be varied due to the enzymatic reaction between GOx and glucose, resulting in a shift in the SPR spectrum with various glucose concentrations. Moreover, it was reported that sensitivity of 0.854 nm mg^{-1} dl^{-1} could be achieved with high selectivity and stability, which has shown great potential for application with CGM in the near future [67].

In addition, Yuan *et al* [68] have presented a reflective SPR optical fiber with a layer of glucose-sensitive membrane, where GOx was embedded in PAM gel modified with SiO_2 nanoparticles. As shown in

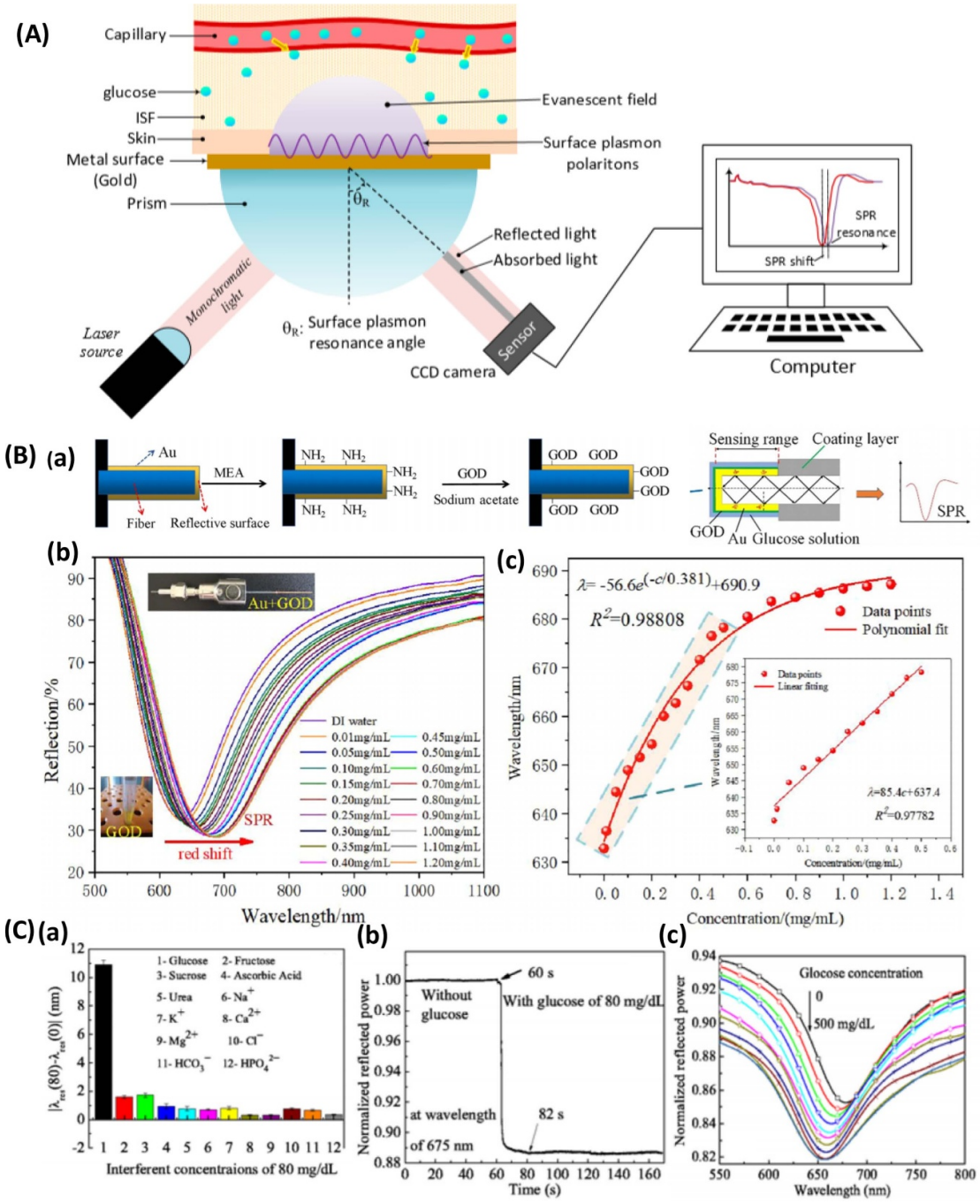

Figure 10. Optical glucose sensing via SPR. (A) Schematic diagram of SPR technology based on the Kretschmann configuration. Reproduced from [53]. CC BY 4.0. © 2019 by the authors; licensee MDPI, Basel, Switzerland. (B) Characterization for reflective SPR optical fiber with GOx immobilized via covalent binding including (a) a schematic diagram of the fabricated sensor, (b) reflection spectra for various glucose concentrations between 0–1.2 mg ml^{-1} and (c) fitting curve with detection range analysis for glucose concentration measurement. Reprinted from [67], Copyright (2020), with permission from Elsevier. (C) Characterization for reflective SPR optical fiber with GOx embedded membrane including (a) selectivity, (b) response time at the wavelength of 675 nm and (c) reflection spectra. Reproduced from [68]. CC BY 4.0. © 2017 Optical Society of America.

figure 10(C), promising results have been achieved in the characterization of this novel optical fiber with high sensitivity, high selectivity and quick response time. On the other hand, Yuan *et al* [69] have investigated a boronic-acid-functionalized SPR optical fiber modified with Au nanoparticles, which could achieve a significantly lower detection limit with the detection range covering physiological blood glucose level. The comparison among key characteristics of the researched SPR optical fibres is summarized in table 7.

To conclude, SPR technology has been widely applied in chemical analysis recently, but only limited research has investigated the application of SPR for non-invasive glucose detection due to its high sensitivity to motion, sweat and temperature with limited sensitivity to small glucose concentration [53]. However, new

Table 7. SPR glucose sensors.

	GOx immobilized SPR optical fiber	SPR optical fiber with GOx embedded membrane	PMBA/AuNP modified SPR optical fiber
Function layer	GOx (covalent binding)	GOx (gel embedding)	Boronic acid
Sensitivity (nm (mg dl^{-1})$^{-1}$)	0.854	0.14	N/A
Detection range (mg dl^{-1})	0–50	0–80	0.18–540.5
Detection limit (mg dl^{-1})	0.04	2.1	0.0014
Response time (s)	90	22	N/A
References	[67]	[68]	[69]

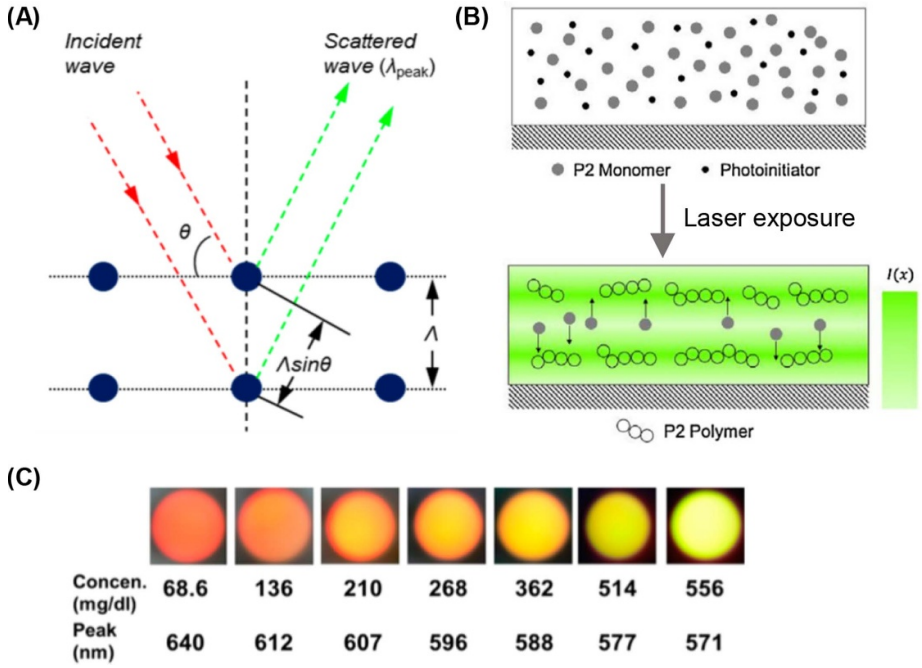

Figure 11. Schematics for holographic sensors. (A) Schematic illustration for Bragg condition. Reprinted with permission from [51]. Copyright (2014) American Chemical Society. (B) Schematic illustration for double-polymerised holographic gratings. Reprinted from [71], Copyright (2018), with permission from Elsevier. (C) Example readout scheme for holographic glucose sensors. Reprinted with permission from [51]. Copyright (2014) American Chemical Society.

researches have been launched to fabricate highly sensitive and refractive optical sensors, to consider solving the problem via advanced nanotechnology and materials science.

4.5. Holography

Holography refers to the technique that could achieve 3D imaging with the application of a light-sensitive material or nanofabrication techniques and the holographic gratings could be fabricated with the exposure to laser light [51]. As a novel type of optical sensing platform, holographic sensors, which have drawn much attention recently, could be narrowly diffracted between UV and NIR range [70].

The optical characteristics of holographic sensors could change with the exposure of analyte. Hence, there are holographic sensors fabricated based on either reflection holograms or transmission holograms [51]. For those based on reflection holograms, the sensors are able to be used visibly under normal light, whose changing diffracted wavelength could be easily observed. For those based on transmission holograms, the results could be obtained from a spectrometer with a changeable wavelength of maximum diffraction efficiency [51]. With the illumination from a white light source, the recorded nanoparticle spacings of the hologram would act as mirrors that follow Bragg's law, as shown in figure 11(A):

$$\lambda_{peak} = 2n_0 \Lambda \sin(\theta), \tag{1}$$

where λ_{peak} refers to the wavelength of diffracted light at the maximum intensity, n_0 refers to the effective index of refraction in terms of the recording medium, Λ refers to the spacing between the recorded layers and θ refers to the Bragg angle according to the geometry [51, 72].

Effort has been put into holographic glucose sensing in recent decades. It has been proved that holographic glucose sensors could be fabricated from phenylboronic acid-based hydrogels, which could reversibly respond to the various glucose concentrations within the visible range [72]. Interference from lactate has been identified and the optimal selectivity has been found with hydrogel containing 20% mole fraction of 3-actrylamidophenylboronic acid (3-APB) [72].

With the application of 3-APB-based hydrogel, a novel holographic glucose sensor structure has been recently investigated with double polymerization, although the optimal response of the sensor still requires further study [71]. As shown in figure 11(B), in this process, a lightly crosslinked phase is formed from 3-APB monomer solution (P1) and then another heavily crosslinked phase is formed from a second monomer solution (P2) for the further generation of holographic gratings [71].

As mentioned previously, the boronic acid derivatives applied should be chosen carefully to minimize the interference from pH. Hence, further investigations on different boronic acid derivatives have been undertaken and it has been revealed that the 2-acrylamidophenylboronate appears to be a promising candidate for better selectivity in physiological pH range [51]. Besides, *in vitro* studies have been undertaken for the quantitative analysis of blood glucose concentration within the visible range and the colorimetric results are shown in figure 11(C) below. It has been proved that holographic glucose sensors are able to provide accurate results and do not suffer from major lags and interference [51].

More recent researches have been conducted by fabricating the holographic glucose sensors via laser ablation with 4-formylphenylboronic acid-functionalized hydrogel, whose performance has been evaluated within both the visible and NIR region [36]. A novel holographic glucose sensor was fabricated with laser ablation on gold-nanoparticle-modified chitosan hydrogel, covering the full physiological glucose concentration [36]. Moreover, there was little potential interference found from fructose, vitamin C and lactate present in ISFs and the sensor was found to be stable to the variations in temperature, pH or ionic strength of the environment [36]. As discussed in previous sections, the boronic-acid-functionalized hydrogels were considered to be highly sensitive and biocompatible, which shows promising results for the potential application for implantation, although further validation on *in vivo* applications is necessary.

5. Other glucose-sensing methods

5.1. Microwave

Microwave has attracted much attention as it can deeply penetrate the tissue and easily reach the point where more accurate glucose measurement could be obtained with sufficient blood concentration [53]. There are three basic principles involving microwave available that could be applied to glucose monitoring by a near-field sensor, including reflection, transmission and resonant perturbation [73]. The reflection method measures the reflection parameter, S_{11}, for the determination of amplitude and phase variation resulting from the changing permittivity of blood with various glucose concentrations, while transmission methods measure a full set of S parameters including the transmission parameter, S_{21}, allowing complex calculations for more accurate results [53]. The resonant perturbation method, on the other hand, measures the variation of resonant frequency, quality factor and 3 dB bandwidth for the correlation [53]. However, all these methods are limited to their specific working frequency while suffering from the interference of changes to the environment due to the high sensitivity [73].

As shown in figure 12(A), Odabashyan *et al* [74] have developed a Hilbert-shaped microwave sensor, measuring the concentration of glucose in aqueous solutions by determining the transmission parameters, where a detection limit of 1.92 mg dl^{-1} has been obtained at the operating frequency of 6 GHz. Moreover, the temperature dependence of the sensor has also been tested and reasonable temperature correlation coefficients were obtained within the detection range of 50–150 mg dl^{-1}.

To achieve the aim of non-invasive CGM, it is of great importance that the glucose sensor under research could not only be characterized in aqueous solutions, but simulated biofluids such as sweat or ISF for a better understanding of its performance in the real environment. In this case, Baghelani *et al* [75] have investigated the performance of a chipless tag split-ring resonator with mimicked ISF solutions, from which a detection range of 36–450 mg dl^{-1} and detection limit of 0.01 mg dl^{-1} could be achieved at the operating frequency of 4 GHz, with a conceptual diagram of application shown in figure 12(B).

On the other hand, Xue *et al* [76] have presented a nanostrip-based microwave biosensor, aimed atfor non-invasive glucose sensing via sweat. The sensor was developed from microstrip antenna-based microwave sensors for better sensitivity and GOx was immobilized on the nanostrip to enhance the performance, as shown in figure 12(C). The comparison of key characteristics for these sensors is shown in table 8.

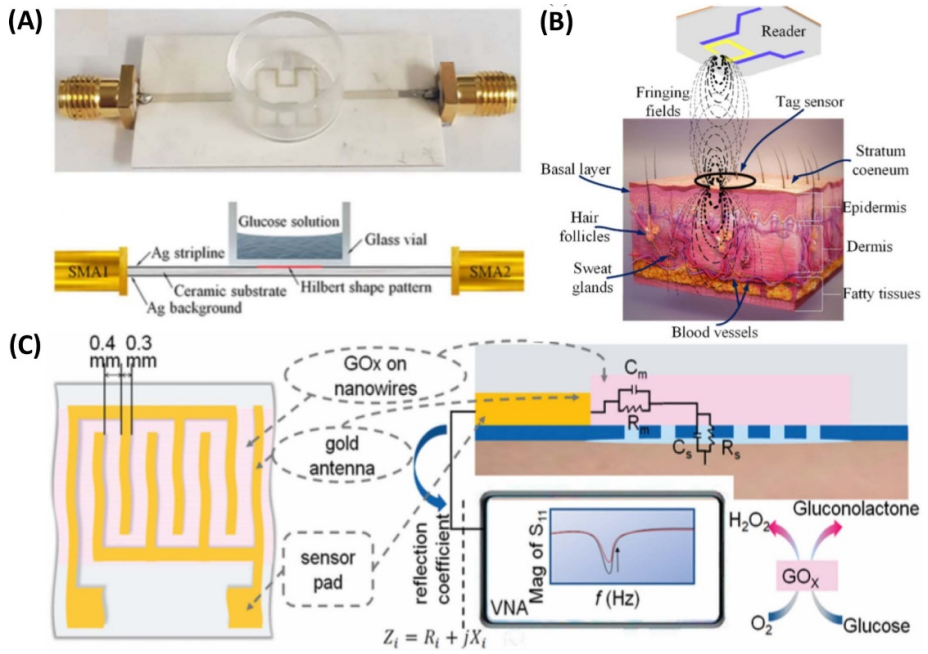

Figure 12. Schematics of the microwave sensor structure. (A) Hilbert-shaped transmission sensor. Reproduced from [74]. CC BY 4.0. © 2019 Optical Society of America. (B) Split-ring resonators. Reproduced from [75]. CC BY 4.0. © The Author(s) 2020. (C) Nanostrip-based reflection sensors. Reproduced from [76] with permission of The Royal Society of Chemistry.

Table 8. Examples of microwave glucose sensors under research.

	Hilbert-shaped transmission sensor	Nanostrip-based reflection sensors	Split-ring resonators
Function layer	Ag	Au/GOx	Cu
Testing fluid	Solutions	Sweat	ISF
Detection range (mg dl^{-1})	50–150	0.02–180	36–450
Detection limit (mg dl^{-1})	1.92	1.8×10^{-6}	0.01
Frequency (GHz)	6	2	4
Key features	• Temperature correlated • Cheap • Easy fabrication	• Enzyme immobilized • Suitable for wearable device	• Suitable for wearable device • Distant communication
References	[74]	[76]	[75]

5.2. Radiofrequency

Radiofrequency (RF)-based biosensor has drawn considerable attention for high-sensitivity glucose detection without the presence of a mediator [77]. Similar to microwave resonators, the glucose concentration could be determined by measuring the shift in resonance frequency with the variation in signal amplitude, where the dielectric parameters could be obtained and correlated with a glucose sample [78]. It is considered to be a promising technology for non-invasive glucose monitoring, as it could avoid suffering from the interference of environmental factors and limited lifetime, which are the critical drawbacks of traditional electrochemical glucose sensors [79]. Moreover, there is no pre-stabilization required and a quick response could be achieved for label-free glucose detection with RF biosensors [79]. Nevertheless, the major concern of this technology is the interference from the presence of liquids in tissue, as the radio signals would be adversely affected by the absorption of liquids [80]. Besides, there is a considerable health risk for potential frequent exposure under RF waves. Hence, further investigation should be undertaken for the minimization of the potential risk [81]. Examples of recent achievements for this technology are shown in table 9 and figure 13.

5.3. Bioimpedance

The idea of bioimpedance has been proposed as one of the potential candidates for non-invasive glucose monitoring, which measures the resistance to electric current flowing through the tissues of a living organism [82]. The permittivity and conductivity of the red blood cell membranes would change with the decrease of sodium and increase of potassium ion concentration, resulting from the variation in blood glucose level [53, 82]. Therefore, bioimpedance spectroscopy could be achieved by applying an alternating

Table 9. Examples of RF glucose sensors under research.

	RF integrated passive device biosensor chip	RF biosensor chip with hammer-shaped capacitors	RF patch biosensor with volume-fixed structures	RF biosensor with air-bridge structure
Function layer	Au	Ti/Au	Cu/Au	Ti/Au
Testing fluid	Sera	Solution	Solution	Serum
Sensitivity (MHz mg^{-1} dl^{-1})	1.99	N/A	1.97	1.08
Detection range (mg dl^{-1})	148–228	50–500	N/A	148–268
Detection limit (mg dl^{-1})	5.9×10^{-4}	8.01	15.22	8.01
Response time (s)	2	0.85	1	N/A
References	[77]	[79]	[80]	[78]

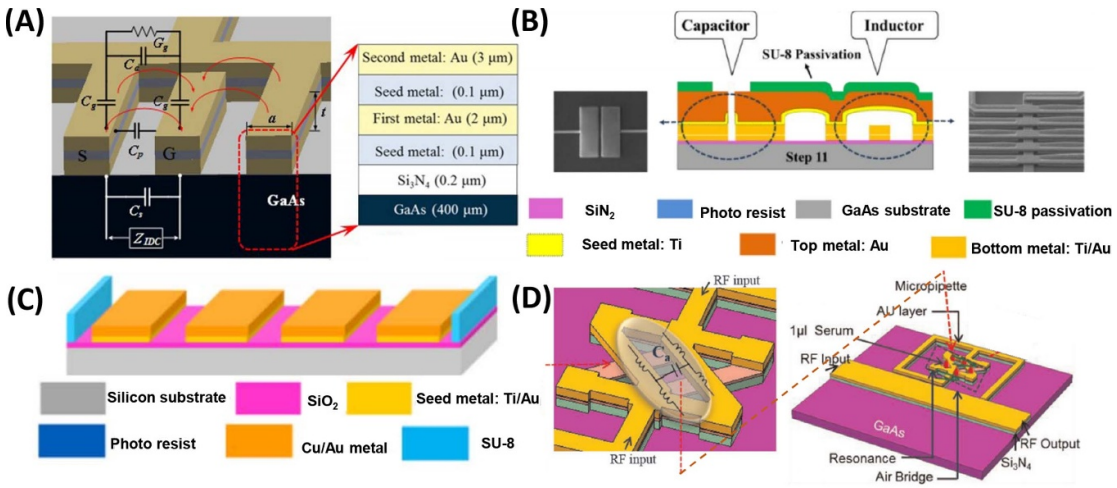

Figure 13. Schematic diagram of the RF biosensor structure. (A) RF resonator for label-free sensing. Reproduced from [77]. CC BY-NC-SA 4.0. Copyright © 2015, The Author(s). (B) RF resonator with hammer-shaped capacitors and spiral inductors. Reproduced from [79]. CC BY 4.0. © The Author(s) 2020. (C) Patch biosensor with a front-side tank. Reprinted from [80], Copyright (2017), with permission from Elsevier. (D) RF biosensor with air-bridge structure. Reprinted from [78], Copyright (2015), with permission from Elsevier.

current for the measurement of corresponding resistance and hence the conductivity could be deduced and directly correlated with the glucose concentration [53]. This method is easier and cheaper to apply compared to others, but its high sensitivity to temperature and body fluids such as sweat remains a great concern [82]. Furthermore, it could be significantly affected by the physiological conditions of the cell membrane [53]. Although it has been proved that it could successfully correlate glucose concentration and electrical properties linearly with only 3.7% error, further research is required to achieve the application in non-invasive CGM [83].

6. Discussion

6.1. Current achievements in glucose-sensing technologies

The key advantages and challenges for the glucose-sensing technologies discussed in previous sections are summarized and shown in table 10 below. Among these glucose-sensing technologies, enzymatic-based electrochemical glucose sensors were the most traditional technique for glucose sensing with the application in most of the currently available glucose monitoring systems in the market, both discrete portable finger-tip monitors or continuous glucose monitors. The research in the field of electrochemical glucose sensors continues for new generations of GOx-based glucose sensors, achieving more efficient electron transfer. Moreover, new electrode materials have been widely researched as alternatives to GOx, especially metal-based, nanoparticle-based or graphene-based materials, which could minimize the interference from the environment and hence potentially improve the performance of electrochemical glucose sensors [38].

For optical sensors, fluorescence might be the most intensively researched technique, with the implantable applications commercially available such as Eversense [53]. However, the unavoidable

Table 10. Summary of common glucose-sensing technologies of interest.

Principle	Category	Advantages	Challenges	Reference
Enzymatic method	Electro-chemical	• Well-researched method • Easy to apply • Good selectivity	• Interference from environment • Reaction mediator required	[28]
Fluorescence	Optical	• High sensitivity • High selectivity • Immune to light scattering	• Interference of pH • Potential toxicity • Short lifespan • Photobleaching and scattering	[57]
NIR spectroscopy	Optical	• High penetration • Low cost	• Low intensity • Complex scattering • Low sensitivity at low concentration	[61]
MIR spectroscopy	Optical	• High sensitivity to glucose • Low scattering	• Low penetration • Strong water absorption	[59]
Raman spectroscopy	Optical	• Easily identified • Less sensitive to water • Less sensitive to temperature	• Long collection time • Unstable laser wavelength	[53]
Photoacoustic spectroscopy	Optical	• Simple • No interference from water • Not affected by scattering particles	• Sensitive to changes in the environment • Limited signal-to-noise ratio • Long integration time	[66]
SPR	Optical	• High sensitivity to glucose change • No need for statistical calibration	• Sensitive to motion and environment • Limited sensitivity to a small concentration	[67]
Microwave	Electrical	• Deep penetration • No risk of ionization • High sensitivity	• Sensitive to biological differences and changes in the environment • Poor selectivity	[74]
RF	Electrical	• Easy fabrication • Quick response • High selectivity • Good linearity	• Interference from the presence of liquids • Potential health risks due to long exposure	[80]
Bioimpedance spectroscopy	Electrical	• Inexpensive • Easy measurement	• Sensitive to sweat and temperature • Interference from environment	[82]

photobleaching and scattering remained a major challenge for *in vivo* applications, which led to investigation of other technologies such as NIR, MIR, Raman and SPR. Boronic acid and its derivatives have been considered as an effective glucose-sensitive compound and an increasing number of researches have focused on boronic-acid-functionalized optical glucose sensors. Boronic-acid-functionalized hydrogels were found to be a highly biocompatible material with great potential for *in vivo* CGM and the boronic acid hydrogel-functionalized optical fibers and holographic sensors were developed as novel optical glucose sensing platforms, although further validation for *in vivo* applications is required for this promising technology.

One of the major challenges of glucose sensing comes from the presence of other molecules in the biofluid with similar optical characteristics to glucose, resulting in the issues of selectivity, sensitivity and interference [53]. Therefore, other frequencies of the spectrum have also been investigated to potentially overcome these issues, including microwaves and RFs. Nevertheless, most of the researches in these fields were still at the early stages, and hence further studies should be undertaken towards the final application in CGM.

6.2. Market analysis for future direction

The current market for continuous glucose monitors has been briefly analyzed via patent research, according to the statistical data taken from the Patent Categorization System [84]. Statistical analysis was performed on

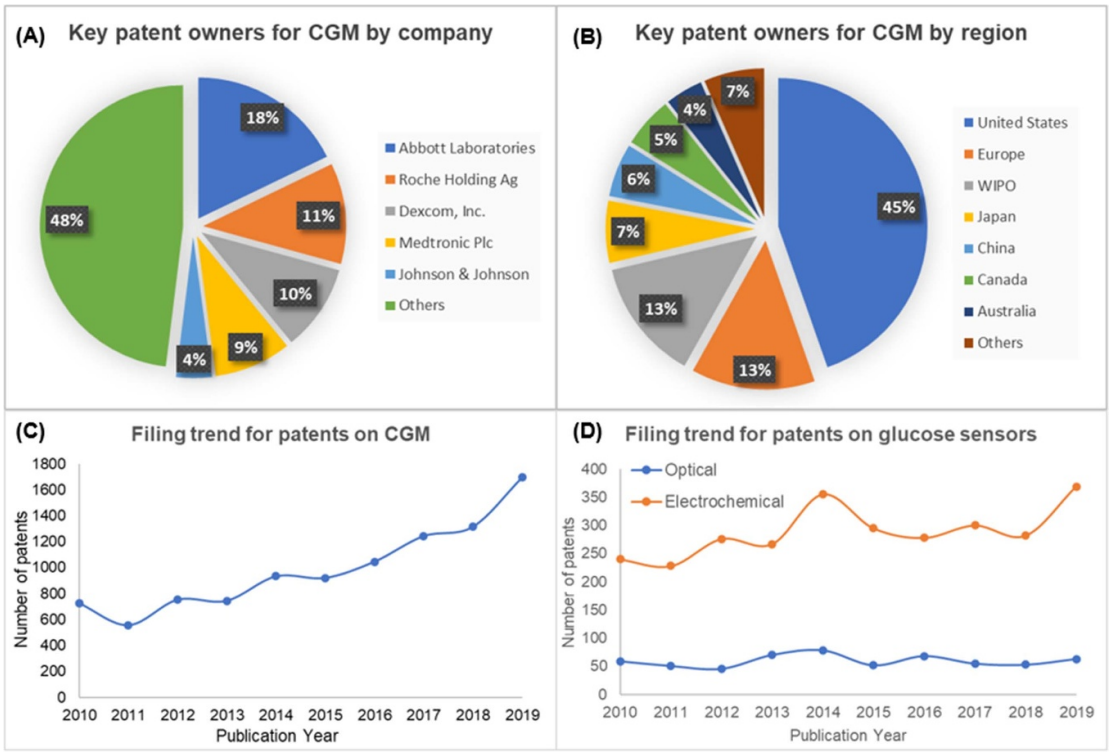

Figure 14. Patents on glucose sensors in the current market: (A) key patent owners for CGM by the company; (B) key patent owners for CGM by region; (C) filing trend for patents on CGM in terms of publication year; (D) filing trend for optical and electrochemical glucose sensors in terms of publication year. All data were taken from the Dolcera Patent Categorization System [84].

key patent owners for CGM in terms of both company and region. As shown in figure 14(A), five well-known global leaders in medical technology have become the key players in CGM, including Abbott Laboratories, Roche Holding, Dexcom, Medtronic and Johnson & Johnson, which owns over half of the market in total. Besides, statistics in figure 14(B) show that the United States played a leading role in investigating the most advanced technologies for CGM, owning 45% of the related patents worldwide, followed by Europe, Japan, China, Canada and Australia as other major regions with considerable achievements in this area. It is notable that the World Intellectual Property Organization (WIPO) also owns 13% of the CGM-related patents in the market, indicating the presence of a great international collaborative in the field of CGM research.

In addition, the filing trends for patents in related fields have been plotted for the past 10 years. It could be concluded from figure 14(C) that an increasing number of researches in terms of CGM have been carried out recently with considerable achievements, although the total number of filed patents are still limited, which indicates that this emerging area has drawn progressively more attention and is worth further investigation. To be more specific, the filing trend for the patents in terms of the two major categories of glucose-sensing technologies, electrochemical and optical glucose sensors, are summarized in figure 14(D) below. It could be seen that the number of published patents for electrochemical glucose sensors is significantly larger than that of optical glucose sensors. Meanwhile, the number of newly published patents for electrochemical glucose sensors have gradually increased overall in the past 10 years, although some fluctuations might be observed with a secondary peak, which appeared in 2014. On the other hand, the number of newly published patents for optical glucose sensors remained steady at a low level during the past 10 years, which indicates that the researches for optical glucose-sensing technologies are still at an early stage. This might be related to the reason that this area is relatively novel and has been less progressive during recent decades. Hence it is of great significance that more effort be devoted to the field of optical glucose sensing towards novel applications for CGM.

6.3. Future developments

Compared to currently available technologies, the new generation of CGM systems would ideally be more accurate, require less frequent calibrations, have a longer lifetime, become more convenient for diabetic patients and hence gain higher patient compliance. However, there are multiple trade-offs to be balanced when developing a novel glucose sensor, including accuracy versus convenience in terms of the calibration

frequency and also comfort versus capability in terms of the sensor complexity [14]. The successful application of implantable fluorescence glucose sensors, as an alternative to the traditional enzymatic electrochemical glucose sensors, could be considered as a significant milestone in the pursuit of a mediator-free non-enzymatic glucose sensor with longer lifetime and less calibration frequency [24].

Nevertheless, it could be seen that there are still major challenges that remain to be solved in the future for CGM. For example, in terms of implantable applications, the ever-present obstacle of the foreign-body response will remain a major technical challenge in the near future. Some considerable attempts have succeeded in minimizing the toxicity and immune response, especially the biocompatible glucose-sensitive hydrogel optical fibers. Moreover, the biomimetic hydrogel could also be considered as a layer of coatings to other types of glucose sensors, which would be promising in reducing biofouling for fully implantable devices [24]. However, those novel materials and technologies still lack *in vivo* validation. Hence, it is of great significance to have more projects launched in this field, working towards final *in vivo* applications.

In addition, non-invasive glucose monitors have also attracted much attention in recent decades, in accordance with the exponential growth of wearable technology for more convenient collection of physiological parameters [53]. However, the accuracy and reliability of these novel technologies have remained questionable and frequent calibrations are often required for the precise correlation to real-time blood glucose concentrations. Future work could possibly be carried out for integrating the currently available CGM systems with the concept of non-invasive or minimally invasive glucose monitoring, although an enormous number of tests should be performed to further explore the potential.

It is obvious that the various types of glucose-sensing technologies being widely researched have offered great opportunities for a novel type of glucose sensor to be developed, achieving better sensitivity, selectivity, detection limit and detection range. In addition to the traditional electrochemical glucose sensors and well-researched fluorescent glucose sensors, there are also some promising novel optical platforms under research, such as holographic sensors and hydrogel optical fibers. Although most of these technologies are still at an early stage of research with limited experimental results, it is of great promise to achieve higher accuracy, higher biocompatibility and better performance with the assistance of ever-developing materials science.

7. Conclusion

We have provided an overall review for state-of-the-art CGM technologies for the diagnosis and treatment of diabetes. The currently available CGM systems in the market and some applications for implantable glucose monitoring have been introduced and their limitations have been discussed, including their short lifetime, the necessity of calibration, the invasive approach and the foreign-body response. To improve the patient compliance together with the glucose-sensing effectiveness, a large number of non-invasive glucose monitors have been researched with various platforms, such as tattoo, wearable patch, eyeglasses or contact lenses. Furthermore, the biocompatibility of material for the fabrication of sensors has also been researched and hydrogel modified with boronic acid with its derivatives is considered a promising material for *in vivo* CGM applications.

The advances in common glucose-sensing technologies currently being researched have been largely reviewed and summarized. It could be concluded from the literature that increasing effort has been devoted to developing a more effective non-invasive real-time CGM. Electrochemical sensors are the most traditional type of glucose sensors, which are currently applied in various commercially available glucose monitors. Although most traditional electrochemical sensors are enzyme catalyzed, novel material-modified electrodes have been developed, especially metal, nanoparticles or graphene-modified electrodes, aimed at a more effective glucose-sensing performance as alternatives to the presence of the enzyme.

As an alternative to the electrochemical sensors, optical glucose sensors have attracted much attention recently because of their longer lifetime and less lag time for readouts. In addition to GOx, ConA and boronic acid have also been considered as effective glucose recognition compounds, which have been widely applied in optical glucose sensors. Fluorescence is the most researched type of optical glucose-sensing technology and the optical sensors designed for NIR, MIR, Raman, photoacoustic spectroscopy or SPR have also been researched to overcome the drawbacks with fluorescence. As a novel type of optical sensor, holographic glucose sensors have also been recently studied and promising results have been shown for its potential to replace electrochemical sensors in the future.

Some other glucose-sensing technologies have also been researched for better selectivity and sensitivity, such as microwave, RF or bioimpedance. Nevertheless, these technologies are still at an early stage of research and much more investigation will be required for the final application in CGM.

Market analysis for newly published patents during the past 10 years indicates that CGM has drawn increasing attention in recent decades and most of the well-known global leaders in medical technology have

been involved in the advanced research in this field with considerable international collaboration. Although the researches for traditional electrochemical glucose sensors have remained progressively with novel materials, those for optical glucose sensors have also been ongoing with considerable progress made every year. With a broad overview of the critical challenges that remain, it could be concluded that more effort is expected to be put into the emerging optical glucose-sensing platforms to improve their accuracy, biocompatibility and performance, which would provide great potential for the final *in vivo* application for CGM in the near future.

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