# Recent advancements in biosensor technology for diabetes monitoring

Xinyang Li

Department of Chemical & Biomolecular Engineering, National University of Singapore, 117585 Singapore

Email: xinyang.li@u.nus.edu

**Abstract.** Diabetes mellitus is a global health concern and its associated complications are a leading course of mortality in the world. In personalized healthcare, the ability to conduct on-demand screening, real-time monitoring, and rapid early-stage diagnosis of diabetes is essential for tailoring effective treatment plans to individual patients. The present research efforts are directed towards achieving miniaturization of analytical equipment and reducing the consumption of reagents. As a result, biosensors have been developed that enable sensitive, selective, accurate, rapid, and cost-effective measurements. This review provides a comprehensive summary of the mechanism employed by each biosensor, as well as some hurdles that currently impede the widespread clinical implementations. Moreover, the recent applications that integrate biosensors for diabetes monitoring are also addressed. Eventually, this paper emphasizes the significance of developing multifunctional hybrid platforms for simultaneous monitoring. The paper underscores the potential of combining machine learning algorithms with artificial intelligence-based decision making to improve overall personalized glucose management.

**Keywords:** Biosensor; Glucose monitor; Diabetes mellitus.

## 1. Introduction

Diabetes mellitus (DM) is a severe chronic ailment that has consistently led to high morbidity and mortality and its prevalence is increasing at an alarming rate. The International Diabetes Federation reported that the global number of individuals afflicted with diabetes in 2021 stood at 537 million, and this figure is projected to surge to 783 million by 2045. There were 6.7 million deaths attributable to diabetes in 2021, reflecting a 46% increase over 2011 [1]. Insufficient insulin levels are a hallmark of DM, and the development of insulin resistance is impacted by a number of variables, including genetics, an active lifestyle, obesity, and exposure to toxins in the environment, all of which can disrupt the production of insulin. People with DM experience unpredictable fluctuations in blood glucose levels and are susceptible to developing severe complications, such as stroke, blindness, and cardiovascular issues. This disease is a widespread disorder, as it significantly affects individuals' living quality. The annual expenditures related to diabetes healthcare exceed billions of dollars, covering medical expenses, medications, blood glucose tests, work absenteeism, etc [2]. These observations indicate that early diagnosis, on-time intervention, and consistent monitoring play a crucial role in enhancing patients' life quality and preventing potential complications.

The history of glucose sensing dates back to 1841 when urine testing was first introduced. However, the connection between plasma glucose levels and urine proved to be unreliable. In contemporary practice, blood glucose monitoring stands as a widely employed method for determining insulin requirements and identifying unusual glucose levels that may indicate illness, dietary adjustments, or unfavorable medication reactions. Although various blood glucose meters are commercially available, they all necessitate multiple finger pricks to collect blood samples. Researchers have further explored minimally invasive or non-invasive techniques, such as infrared spectroscopy, fluorescence spectroscopy, and Raman spectroscopy for blood glucose monitoring. However, it is important to cross-reference these findings with direct blood glucose measurements to ensure accuracy. The sensitivity and reliability are significantly constrained by factors such as the spectral signal-to-noise level [3]. To date, the majority of blood glucose levels have been measured using intrusive tests, which are generally unfavorable due to the discomfort caused by finger pricking, leading to fewer testing frequencies and insufficient glucose level control. Thus, insufficient blood glucose control leads to more complications and increased management expenses. In this context, scientists have dedicated their efforts to innovating of new diagnostic tools to aid diabetic patients. Biosensors present a promising solution for the in vitro diagnosis of diabetes, with a primary focus on measuring two cortical analytes, glucose and glycohemoglobin HbA1c. The capacity to identify particular targets through biological processes and turn them into electrical, thermal, or optical signals distinguishes biosensors as cutting-edge detection technologies. Numerous advantages are offered by this technology, including quick reaction times, mobility, and increased adaptability [2].

## 2. Biosensing Technology

Traditional analytical methods, such as high-performance liquid chromatography (HPLC), mass spectrometry (MS), enzyme-linked immunosorbent assay (ELISA), or enzyme immunoassay (EIA), provide quantitative data but lack qualitative information. Moreover, these methods are associated with drawbacks such as extensive sample processing time, the need for trained personnel, and limitations in the number of samples that can be tested simultaneously. Optical measuring methods like liquid chromatography-mass spectrometry (LC-MS) have been used to measure salivary glucose levels. Nevertheless, due to the expensive chemicals and intricate equipment required, this measurement can only be done in a laboratory. Due to this, this approach is inappropriate for use in everyday activities where individual glucose monitoring is required [3]. In order to get over these restrictions, biosensor-based devices have been developed. These devices have a variety of special benefits, such as improved sensitivity and selectivity for certain targets, quick processing times, user-friendliness, simplicity in usage, and affordability. Additionally, the integration of biological and chemical sensing approaches in biosensors has led to improved signal transduction [2]. Table 1 presents a comparison between the features of traditional methods and biosensing.

**Table 1.** Comparison of conventional analytical and biosensing approaches [2].

| Techniques | Advantages | Drawbacks |
|---|---|---|
| Traditional analytical methods | a) Sensitivity<br>b) Specificity | a) Longer processing time<br>b) Costly<br>c) Sample preparation<br>d) One-time usage<br>e) Need for expertise |
| Biosensor | a) Fast and real-time measurement<br>b) Cost-effective<br>c) Reusable<br>d) Simple procedure<br>e) High sensitivity and specificity | a) Narrow scope of commercial purposes<br>b) Development and synthesis of novel nanomaterials |

## 3. Categorization Of Biosensors

### 3.1. Electrochemical biosensors

The electrochemical biosensor is a common type of sensing device that converts biochemical interactions into an electrical signal through transduction. The electrochemical sensing of glucose was based on the measurement of oxygen consumption by the enzyme-catalyzed reaction. This method involves the biocatalytic activity of specific enzymes, such as glucose oxidase ($GO_X$) or glucose dehydrogenase (GDH). These enzymes catalyze the oxidation of glucose, leading to the production of specific byproducts, such as hydrogen peroxide or reduced nicotinamide adenine dinucleotide (NADH). Meanwhile, these reactions generate electrical currents or potentials, which can be detected by the electrode in the electrochemical sensor. The amount of electrical signal produced corresponds to the concentration of glucose, allowing for the quantification of glucose levels. On the other hand, the nonenzymatic mechanism involves the direct electrochemical oxidation of glucose on specific electrode materials. Ideal candidate electrode materials have inherent redox properties that allow them to directly react with glucose without the need for catalysis. When glucose comes into contact with the electrode surface, it undergoes a redox reaction, leading to the electrons transfer between the glucose and the electrode, which generates an electrical current measurable by the biosensor. The main issue with non-enzymatic glucose sensors is the uptake of intermediates or active molecules from glucose oxidation in the solution, which might limit electrode action. Additionally, non-enzymatic electrochemical sensors exhibit lower selectivity compared to enzymatic sensors, as the electrocatalytic materials face difficulty in specifically catalyzing glucose oxidation [4]. Based on various signal properties, electrochemical biosensors can be classified into four groups: amperometric, impedimetric, potentiometric, and conductometric biosensors. The sensitivity and selectivity are mainly dependent on the biorecognition element. Electrochemical sensors are highly suitable for miniaturization, offering a well-balanced combination of sensitivity, rapid response times, and cost efficiency [2].

### 3.2. Nanotechnology and Nanomaterials

Over the past two decades, biosensors have been extensively employed in environmental monitoring, food chain safety management, and biohazards detection. The integration of nanotechnology has revolutionized biosensing, leading to the improvement of advanced sensors and mechanisms that enhance overall performance. Recent advancements in nanotechnology have opened up possibilities for constructing nanoscale structures and devices, including nanotubes, nanowires, and nanorods. Compared to traditional biosensors, nano-devices have remarkable electrical conductivity and better optical and magnetic characteristics, which promise greater sensitivity and quicker reaction times. These improved biosensing systems can effectively detect changes in localized micro-environments, providing valuable insights into disease progression and treatment effectiveness. Despite their remarkable benefits, nano-biosensors face certain limitations, such as drift, lack of specificity, and the presence of non-uniform signals. Nevertheless, utilizing glucose biosensors to measure blood glucose levels remains one of the most reliable ways in the early detection of diabetes. Significant research efforts have been directed toward the advancement of diagnostics and biosensors by leveraging the unique properties of nanomaterials. These materials encompass a range of substances, including graphene, quantum dots, carbon nanotubes, metal, and magnetic nanoparticles [5].

### 3.3. Immunosensors

An immunosensors is a type of affinity-based analytical biosensor that detects specific target antigens by forming stable immunocomplexes with capture antibodies, generating detectable signals through a transducer. The effectiveness and reliability of immunosensors are significantly influenced by the specificity, stability, and sensitivity of the antibody. The immobilization of the antibody on the solid surface allows for system reproducibility, which requires the repeated dissociation of the covalent linkage between the antigen and the enzyme from the antibody-immobilized surface to maintain system activity. However, the cost of developing and manufacturing immunosensors can be expensive, limiting their accessibility for some healthcare systems. Additionally, interference from other compounds found in the biological matrix might affect the immunosensor's sensitivity, resulting in unreliable findings. Immunosensors may have limited stability and shelf life, needing periodic calibration and maintenance, which might be time-consuming and call for specialist knowledge. Despite these challenges, ongoing research seeks to improve sensor performance and enhance the overall user experience in diabetes monitoring [2].

### 3.4. Optical biosensors

An optical biosensor is a device that utilizes optical principles to detect and quantify specific targets. The detection mechanism is based on the interaction between the target analyte and a biomolecular recognition element, such as enzymes and aptamers, immobilized on a sensor surface. When the analyte binds to the recognition element, it induces a change in the optical signal, which is measured and correlated to the concentration of analyte. Optical biosensors have found various applications in diabetes monitoring. These biosensors can measure glucose levels in bodily fluids without the need for traditional invasive techniques. The advantages of optical biosensors in diabetes monitoring include their real-time and continuous monitoring capabilities, rapid detection, and the potential for miniaturization, leading to portable and wearable devices. Despite their advantages, optical biosensors have certain limitations. Regular calibration and maintenance are essential to ensure accurate and reliable measurements. Although this approach offers noninvasive monitoring, some devices may still require periodic calibration or cross-validation with traditional techniques. The development and production costs of these sensors may be expensive, and some optical materials may have a limited shelf life or stability [2].

## 4. Applications Of Biosensors In Glucose Monitoring

Glucose sensors utilize biomedia such as interstitial fluid (ISF), sweat, and saliva as non-invasive alternatives for continuously detecting and monitoring glucose levels and temporal profiles. ISF encompasses the space surrounding the cells in tissues and serves as a medium for exchanging dissolved substances with blood capillaries. It helps carry vital substances to the cells, including metabolites, proteins, nutrients, and waste materials, and it also improves cellular respiration. Glucose serves as a significant source of cellular energy and is transported through the bloodstream and ISF. One promising method for glucose monitoring involves collecting ISF samples using reverse iontophoresis (RI) and subsequently detecting extracted ISF glucose through electrochemical means. In RI, two electrodes are placed on the skin’s surface, typically on an area with a rich supply of ISF. An electrical potential is applied, which creates a flow of ISF toward one of the electrodes. The electroosmotic flow that is induced by this current makes it easier for analytes and metabolites to travel from the body to the skin's surface. Due to the skin’s inherent negative charge, positively charged and neutral ions flow toward the cathode, while negatively charged molecules move toward the anode. The neutral charge of glucose molecules in ISF makes them ideal for quantification on the cathodic side through RI collection [6]. Numerous investigations have showcased the utilization of an RI system to achieve ISF glucose level monitoring. For example, researchers evaluated a wearable device featuring an iontophoresis terminal and an enzymatic sensor (Figure 1). To prevent skin irritation, the patch, which was attached to a printed circuit board, used a low current density and a quick reverse iontophoresis time. The device revealed a good association with blood glucose levels when a constant potential step was used. The researchers aim to extend the operation time and transform current readings into concentration magnitudes for an enhanced correlation with glucose levels in blood [7]. It is worth noting that while RI shows great potential as a non-invasive monitoring technique, they also face significant challenges. For instance, the necessity for hydrogel membranes to shield the iontophoresis compartment from direct skin contact. These membranes must be present in order to efficiently capture the modest quantities of ISF produced during the IR process. But dilution effects might result from this configuration, which would be problematic for all IR platforms [6].

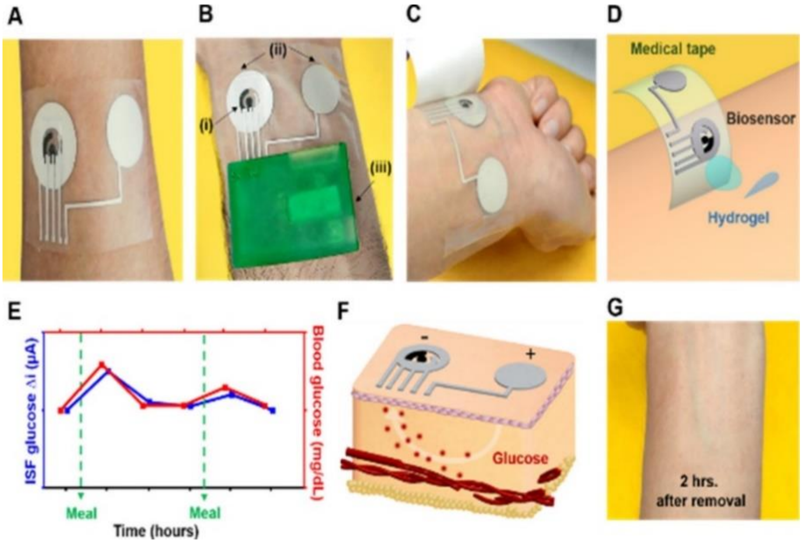


**Figure 1.** Concept of a wearable adhesive patch for glucose detection [7].

Human sweat is a vital biofluid for non-invasive and continuous monitoring applications due to its unique characteristics. It stands out as the most easily accessible source of glucose, offering numerous sampling sites external to the body, thereby ensuring consistent availability. The simplicity of collecting sweat, placing the monitoring device, and the presence of physiologically significant electrolytes and metabolites further enhance its attractiveness for continuous monitoring applications. Notably, sweat contains various metabolites, including glucose, which is a crucial biomarker due to its close relationship with diabetes. This technique can be performed either by direct skin surface interfacing or through microfluidic channels with pre-sampled sweat. Sweat glucose monitoring has been shown to provide accurate reflections of blood glucose levels after proper collecting to prevent contamination for personal variations [6]. Recently, multiplexed sensor arrays have been integrated into wearable devices for sweat glucose monitoring (Figure 2). To concurrently detect metabolites, the researchers fabricated an intelligent, flexible sensor array that connects with the skin. The glucose sensor, utilizing the gold electrode with a Prussian blue layer as a mediator, demonstrated a detection limit of approximately 200μM during in vitro testing. During on-body testing at varying exertion levels, the glucose concentration peaked at around 60-90 μM. Furthermore, this device incorporated a smart circuit board with Bluetooth modules, enabling data sharing or uploading to cloud servers. This device has the potential to be adapted or modified for on-site analysis of various biomarkers present in sweat and other human biofluid samples, enabling personalized physiological and clinical investigations [8].

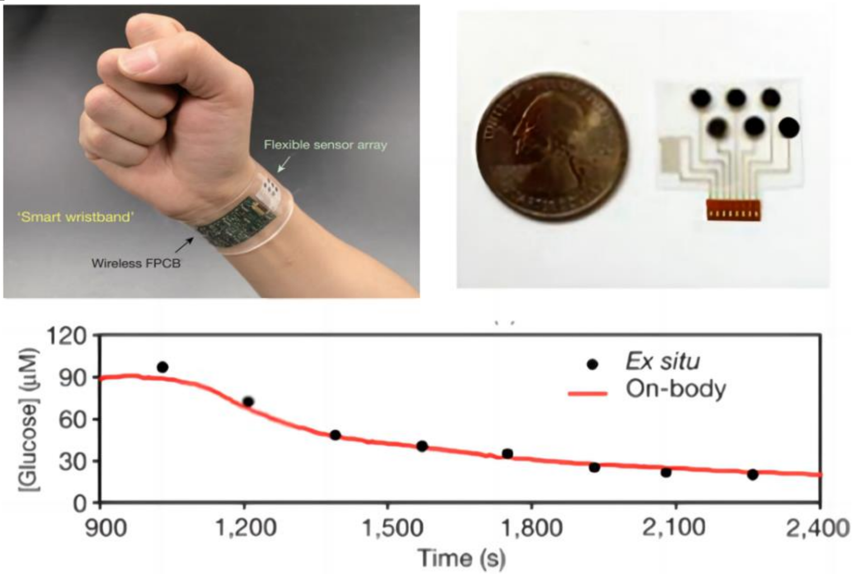


**Figure 2.** Multiplexed sensor arrays for diabetes monitoring [8].

Due to its easy accessibility, abundance of disease indicators, and tremendous potential as a bio-medium for clinical diagnostics, saliva stands out among other biofluids and is particularly well-suited for disease monitoring. Collecting saliva is easy for individuals without puncturing the skin, significantly reducing test discomfort. Changes in saliva compositions, such as amino acids, nucleotides, and microorganisms, are believed to reflect an individual's overall wellness. This correlation makes saliva an attractive candidate for monitoring health and disease conditions in a less invasive manner. The diagnostic potential has been demonstrated for various analytes, including glucose, hormones, and HIV antibodies. In comparison to other biomedia, saliva showed greater sensitivity, particularly in distinguishing smokers from non-smokers and detecting oral cancer. In 2017, a pioneering wearable device integrated into a mouthguard allowed for saliva glucose determination (Figure 3A). The device included a saliva biosensor that allowed amperometric glucose detection using synthetic saliva, together with a modified platinum electrode and glucose oxidase. A wireless measurement system could monitor glucose levels continuously because the detection range was from 5 to 1000 μM [9]. Then, in 2018, a brand-new technique for detecting glucose was unveiled. It makes use of a modified membrane that reacts to changes in its environment, particularly in the oral cavity. The system consists of two resonators connected by the functionalized membrane, which was attached to the human tooth (Figure 3B). The sensor employed broad-side coupled resonators with a silk film and responsive hydrogel interlayer. The hydrogel underwent changes in its thickness and dielectric constant upon absorption of the surrounding solvent, which resulted in modifications in both resonant frequency and signal amplitude. Notably, the frequency modifications indicated the membrane's ability to detect biomolecules, including glucose [10]. With its potential to provide valuable insights into physiological and clinical status, saliva-based diagnostics hold great promise for advancing personalized healthcare.

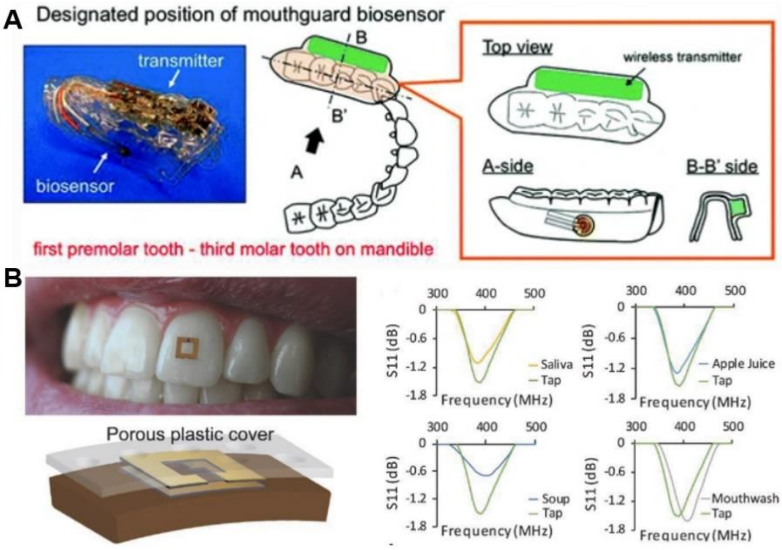


**Figure 3.** (A) Salivary mouthguard biosensor [9]; (B) Implantable salivary biosensor in human teeth and the interlayer response to different liquids [10].

## 5. Conclusion

Based on the official statistics on the prevalence of diabetes, it stands as one of the most critical global health concerns. The disease is closely associated with individual genetics and lifestyle factors, leading to its rapid progression worldwide. Consequently, there is a high demand for fast and user-friendly technology that can effectively detect biomarkers, to control disease outbreaks and manage disease advancement. Biosensor technology has showcased remarkable abilities in identifying diseases, such as diabetes. In this paper, the discussion focused on the categorizations of biosensors, highlighting their sensing mechanisms, as well as identifying obstacles that hinder their commercialization. Moreover, several case studies have been performed to renovate and optimize wearable glucose sensors with proper mechanisms to enhance the detection limits. ISF, sweat, and saliva have all been considered as possible biomedia for monitoring glucose levels and assessing their correlation with glucose concentrations found in blood. These studies have provided valuable insights for research communities to enhance their understanding of the relationship between glucose and other relevant biomarkers, as well as the associations with their blood levels.

In conclusion, continuous glucose monitoring has been assessed in various noninvasive biomedia. Multiple investigations have shown that there is a significant link between ISF and blood glucose levels. Other wearable platforms, such as RI- and microneedle-based devices, are being researched for ISF glucose detection in addition to the commercial glucose monitors. However, it is essential to tackle stability issues, such as biofouling, when performing measurements using microneedle-based devices. Glucose levels in sweat have been assessed during exercise and rest. Different sweat sampling approaches may influence the relationship with blood glucose level, necessitating a unique large-scale validation to take into account individual variances. To accurately estimate glucose levels in saliva, it is important to account for the risk of contamination from glucose residues present on the skin or in the mouth. However, it has been shown that there is a significant association between blood glucose levels and those observed in perspiration or saliva by resolving issues with sample collection. Therefore, these biofluids need additional research and comprehensive validations to determine their connection with the benchmark glucose levels present in blood.

While significant breakthroughs have been made in the field, there are immense opportunities in incorporating glucose sensing with biophysical sensing, which would enable the simultaneous monitoring of both chemical and physical changes. It is vital to monitor physiological indicators such as glycosuria and blood pressure as diabetes directly impacts them. Therefore, there is considerable potential for developing such multifunctional hybrid platforms. Furthermore, the management of diabetes could be significantly improved by developing wearable devices that can simultaneously monitor significant biomarkers for diabetes, such as insulin and ketones. Insulin serves as an indicator for diabetes management as fluctuation in insulin levels can significantly impact glucose metabolism. Continuous and noninvasive insulin levels monitoring poses significant difficulty due to the low concentration of insulin in the blood. Ketones are directly related to the ketogenic diet, making their monitoring necessary for personalized nutrition management. However, the product capable of monitoring ketones alongside glucose is still in its developmental stage. Hence, it is crucial to prioritize the development of multiplexed sensing devices that can simultaneously monitor multiple biomarkers for glycemic control. Lastly, the considerable volume of data generated by glucose sensors can be processed and analyzed using machine learning algorithms, leading to the development of decision-making systems based on artificial intelligence. This advancement has great potential to enhance diabetes management by delivering personalized and precise insulin dosing to individuals. Ultimately, the future of diabetes management is expected to be revolutionized by fully automated personalized artificial pancreas systems that combine machine learning decision-making algorithms. Success in glucose sensors relies on collaborative efforts from different fields, such as engineering, data science, and nutrition. Therefore, it is of utmost importance to emphasize both fundamental research and the commercialization of biosensors to develop rapid, robust, sensitive, user-friendly, and point-of-care tools for effective diabetes management.

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