chemosensors

Review

The Development, Characteristics, and Challenges of Biosensors: The Example of Blood Glucose Meters

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Abstract

Numerous research projects on biosensors have been conducted, and a substantial number of academic studies and conference papers on biosensors are published annually. However, only a few biosensors have been commercialized. In this review, we took blood glucose meters as an example to review the development, characteristics, and challenges of biosensors in the literature. The four subsystems of the physical sensors are illustrated to emphasize the importance of standardization and traceability in the sensors. The development of physical sensors, chemical sensors, and biosensors is introduced. The importance of reference materials as a standard for evaluating sensor performance is emphasized. The basic technique and four types of chemical transducers are described, and we show that the biosensors' response must be processed with these chemical sensors. The characteristics of the glucose meter are introduced to explain the success of this sensor, especially the sensing materials of glucosidases. Two types of highly developed and competitive biosensors, continuous glucose monitoring (CGM) and paper-based biosensors, are introduced, and the trends and future implications of both biosensors are illustrated. The challenges facing biosensor development are summarized into several key factors, and future research directions are discussed. A list of factors for the successful commercialization of biosensors is also proposed.

Keywords: physical sensors; chemical sensors; transducers; biosensors; challenges; glucose meter; reference materials

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1. Introduction

Sensors play a vital role in modern technology and society. Their importance lies in their ability to detect, measure, and respond to physical, chemical, and biological changes in the environment. Sensors bridge the physical world and digital systems, making them indispensable in virtually every field, including engineering, medicine, transportation, environmental science, and beyond. Their importance continues to grow as we move toward more intelligent, connected, and automated systems.

According to statistics, the global sensors market is projected to reach USD 240.6 billion by 2024. The market values of physical, chemical, and biosensors are USD 160.2 billion, USD 59.0 billion, and USD 27.4 billion, respectively [1,2]. The percentage of physical, chemical, and biosensors in the world sensors market is shown in Figure 1.

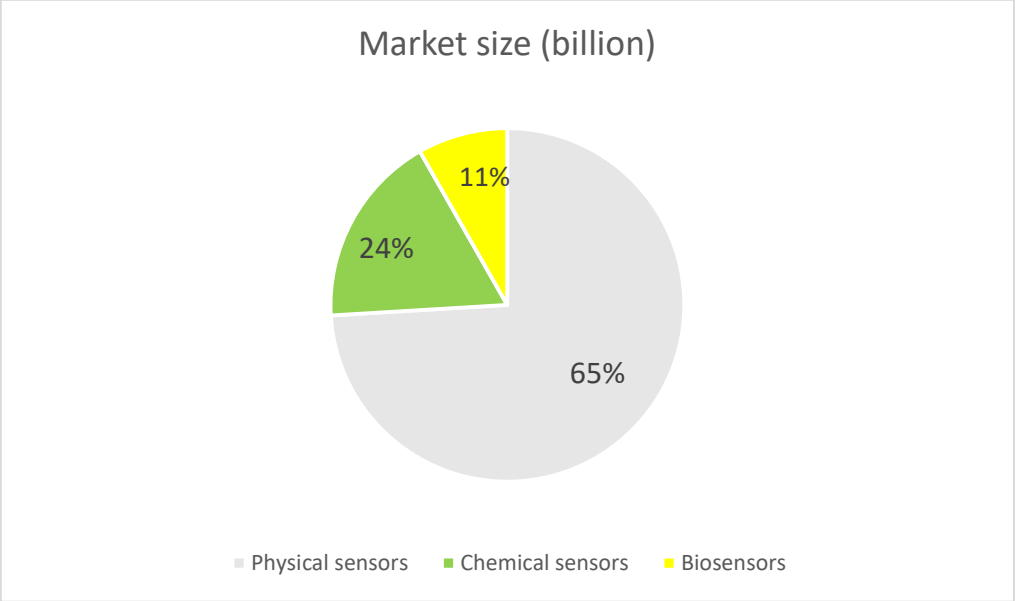


Figure 1. The percentage of physical, chemical, and biosensors in the world sensors market.

The segments of physical, chemical, and biosensors are 65%, 24%, and 11%, respectively. The market share of biosensors has increased year by year [1,2].

Every year, numerous academic studies and conference papers on biosensors are published; however, only a limited number of biosensors have been commercialized to date.

Commercially available biosensors have been introduced in various fields, including clinical diagnostics, food quality control, bioprocess monitoring, and biotreatment [3].

Numerous books have been written to introduce the development of biosensors [3–10]. Many excellent biosensor review studies have been published [11–17]. Some well-known commercialized biosensors are introduced as follows:

1. Glucose biosensors for diabetes management. These sensors use glucose oxidase to detect glucose in blood or interstitial fluid and are widely used in blood glucose meters and continuous glucose monitors (CGMs) [18–20].
2. Pregnancy tests (hCG tests). These are used for home pregnancy testing. They use a lateral flow immunoassay to detect the hormone hCG in urine [21,22].
3. COVID-19 rapid antigen tests. These tests are used to detect SARS-CoV-2 antigens. They use the lateral flow assay with antibodies to detect viral proteins [23,24].
4. The i-STAT system, which is applied in point-of-care diagnostics, such as blood gases and electrolytes [25–27].

The global biosensors market was estimated to be worth USD 27.4 billion in 2024 [1,2]. The market values of glucose monitoring, pregnancy test strips, COVID-19 rapid antigen tests, and other biosensors are USD 15.34 billion, USD 1.7 billion, USD 6.2 billion, and USD 4.1 billion, respectively [28–30]. The percentage of these biosensors in the world biosensors market is shown in Figure 2.

The percentages of the glucose monitoring, pregnancy test strips, COVID-19 rapid antigen tests, and other biosensors are 56%, 24%, and 15.2%, respectively. However, as the COVID-19 pandemic was gradually brought under control, the market sales volume of COVID-19 rapid antigen tests gradually decreased. There are still numerous opportunities for biosensors to be commercialized and enter the sensor market, so the challenges associated with commercial biosensors should be considered.

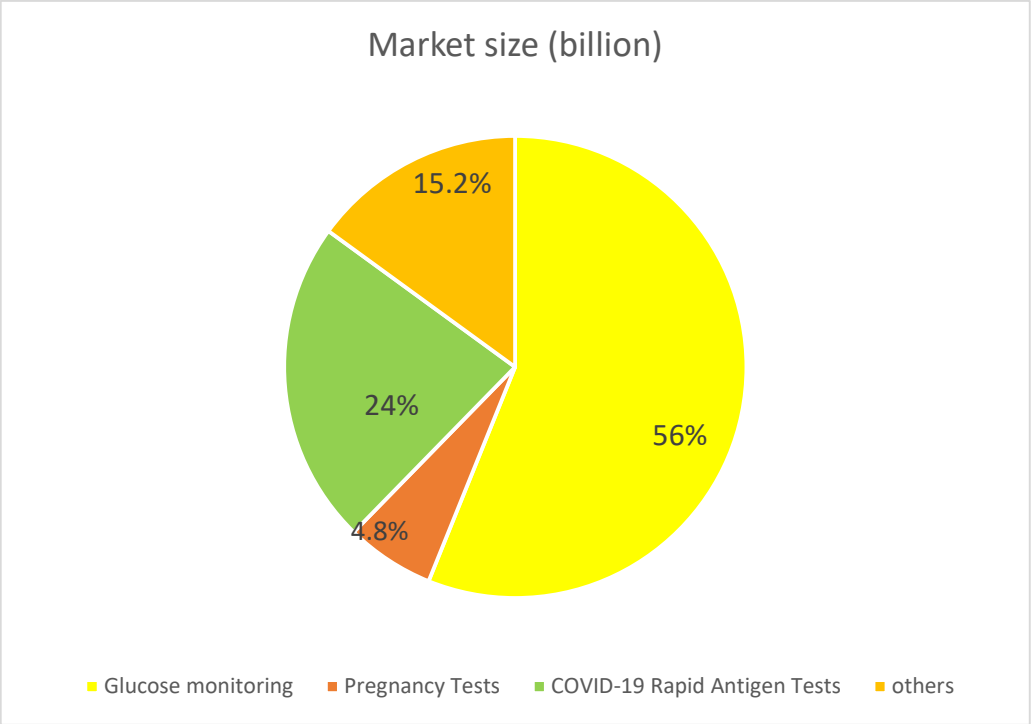


Figure 2. The percentage of these biosensors in the world biosensors market.

The challenges related to biosensors, as presented in the literature, are as follows.

Bhalla et al. [31] introduced the components and development history of biosensors. Biosensors have been under development for nearly 60 years, since 1966. A large number of studies have been published in this field. However, electrochemical glucose biosensors, lateral flow pregnancy tests, and COVID-19 virus tests are among the most commercially available biosensors worldwide. The authors suggested the following difficulties in translating academic research into commercial products: intensification of market needs, testing the sensors' performance in use and after storage, ensuring proper function after six months of storage, stability, costs, and ease of manufacturing each component of the biosensor [31].

In 1956, Leland C. Clark Jr. developed the first oxygen detectors [3,9,10]. In 1962, Clark demoted an amperometric enzyme electrode to detect glucose. Eventually, Yellow Spring Instruments (YSI) developed the first commercial biosensors in 1969. Until now, glucose biosensors have occupied the central biosensors market [32].

The challenges of sample preparation for biosensors using biological samples have been discussed in detail [33]. Martinkova et al. [34] note that biosensors require complicated procedures, demanding preparation time and an expensive technique. They suggest using other devices, such as smartphone cameras, to recognize biosensors' responses.

The success of the glucose meter is due to its high accuracy, precision, and ease of use; this success is not coincidental [3]. Researchers comment that the greatest obstacle to the market availability of biosensors is the lack of a perfect biomarker specific to a signal cancer type. Without requiring electrical devices, paper-based strip technology has been developed for various targets, including human chorionic gonadotropin, C-reactive protein, human immunodeficiency virus, influenza, and multiple cancer biomarkers. Paper strip biosensors are detection systems that protect human beings and are more readily accepted [3,18,20].

The stability problem of biosensors has also been mentioned [35]. Shelf stability is related to the activity retention of enzymes, proteins, and other sensing elements. The major influencing factor is the storage environment. Operational stability involves the reusability of a device. The mechanisms of inactivation determine the operational stability.

For single-use, disposable biosensors, such as glucose meters, shelf-stability is the key issue. For multi-use biosensors, both types of stability should be considered.

The procedures of moving biosensor technology from research laboratories to the market have been reported [36]. Photosynthetic-based biosensors served as an example of the challenges and possible opportunities for environmental applications.

The mechanistic principles of electrochemical impedance spectroscopy-based biosensors for protein cancer biomarker assays have been reviewed [37]. The authors noted the requirement for the device to be applied in clinical practice, not only to test the biosensors on the target analyte, but also to consider the effect of other body fluids. That is, the samples that contained all possible analyses should be used to test the performance of the biosensors, rather than testing the sensors with only the target analyte [37].

The available clinical biosensors and their characteristics are listed in [14], and it was found that only some biosensors are commercially available, such as glucose, pregnancy, and BOD biosensors.

Neethirajan et al. [38] noted that the obstacles to commercializing biosensors included mass production, sensor lifetime, component integration, and practical handling. This limitation is because most biosensor technologies are only in the early stages.

The vision of using paper-based biosensors for rapid and simple clinical diagnostics was emphasized [39]. However, the limitations of commercialization include high limits of detection, inadequate specificity, poor reproducibility, and instability over long-term storage. The increase in the signal-to-noise ratio and the shortening of the detection time are also issues that need to be addressed to compete with the diagnostic tools used in medical systems nowadays.

Dos Santos et al. [40] reviewed the challenges associated with wearable biosensors. In addition to the problems of biocompatibility and energy self-sufficiency, the main challenges of wearable biosensors are the specificity for target analysis due to the complexity of biological fluids, and the sensitivity required to detect different concentrations of the target analyte.

A notable gap was observed between the numerous scientific reports on biosensors and the number of commercially available products [41]. The gap is related to the difficulties of manufacturing robust and reliable devices with specificity, sensitivity, long-term stability, and reproducibility on a large scale.

Numerous electrochemical biosensors have been developed for the ultrasensitive detection of clinical biomarkers [42]. These systems usually lose their performance in the heterogeneous samples. Their operations are too complex for the end users. Many methods have only been developed and tested with clean buffers and purified targets. Romanholo et al. [43] studied the main reliability issues in developing biosensors. They noted that the limitations of these biosensors include a lack of stability, a decrease in catalytic activity over time, and the impact of the ambient environment's expense. The following problems need to be solved to promote the commercialization of biosensors: (1) how to increase the stability of biosensors; (2) how to eliminate cross-reactivity; and (3) how to increase sensor selectivity in the complex matrix.

The intrinsic properties of glucose oxidase, which contributed to the success of the glucose meter, were highlighted in one study [44]. The glucose enzyme is inexpensive, has a rapid turnover, and exhibits high stability at the physiological pH and temperature conditions of human blood.

The reproducibility of transducers is a challenge for the development of transducers [40]. For electrochemical transducers, the adsorption of the analyte, the reproducibility of fabrication, and the resistivity of conductive inks are all key issues. For optical transducers, the variability in color intensity and interference from matrix components are the main challenges [45].

A technique for validating the performance of a novel sensor has been suggested [46]. A new sensor must be tested on various unmodified, unspoken samples. It also requires cross-validation with a reference method. For example, gas sensors may be validated with GC-MS.

The summary of the challenges associated with biosensors is listed in Table 1.

Table 1. Summary of the challenges associated with biosensors.

Category	Challenges	Sources
Commercialization Gap	Few biosensors (e.g., for glucose, pregnancy, and COVID-19) have been widely commercialized despite a vast number of research publications	[14,31,41]
Market Translation	Difficulty in testing long-term performance High production costs Need for scalable, easy-to-manufacture components	[31,36]
Sample Complexity	Biological samples are heterogeneous. Performance varies between real and laboratory conditions High specificity required	[33,37,40,42]
Device Stability	Enzyme/protein degradation over time Shelf stability (for disposable use) Operational stability (for reusable devices)	[35,43]
Sensitivity and Specificity	High detection limits Cross-reactivity in complex matrices Inadequate specificity in real samples	[39,40,42,43]
Reproducibility	Fabrication inconsistencies Signal variation in optical and electrochemical transducers Environmental influence on measurements	[40,43,45]
Integration and Scalability	Difficulties in component integration Lack of robust and scalable manufacturing for large-scale production	[38,41]
Ease of Use	Complex sample preparation Lengthy procedures Complex operation for end users	[34,42]
Analytical Validation	Need for real-sample testing Cross-validation with standard methods (e.g., GC-MS for gas sensors)	[37,46]
Wearable and Portable Sensors	Biocompatibility issues Power requirements Difficulty detecting targets in low concentrations within biological fluids	[40]
Transducer Limitations	Electrochemical: reproducibility, ink resistivity Optical: color intensity variation, matrix interference	[45]
Biomarker Challenges	Lack of specific, validated biomarkers (e.g., for cancer types)	[3,43]
Detection Time and Signal Quality	Long detection time Low signal-to-noise ratio	[39]
Environmental Sensitivity	Ambient conditions affect sensor performance Expensive to maintain sensor activity	[43]

In this review of the development, characteristics, and challenges of biosensors, the background of the challenges associated with biosensors is introduced in Section 1. Section 1 describes physical sensors, chemical sensors, and biosensors. Section 2 describes the characteristics of the glucose meter, explaining the success of this sensor, particularly the sensing materials of glucosidases. Section 3 describes two highly developed, competitive trends and future implications for biosensors. The challenges of developing biosensors are discussed in Section 4. Future trends in glucose detection are introduced in Section 5. Finally, in Section 6, the conclusion presents a list of factors that contribute to the successful commercialization of biosensors.

1.1. Physical Sensors

Many textbooks on measurement principles are available [8,47–49]. Bentley [47] breaks down the measurement system into four subsystems and then explains how to integrate these four subsystems into a measurement system. Standard physical sensors include thermistors, thermocouples, potentiometers, deflection accelerometers, servo-accelerometers, strain gauges, humidity sensors, and piezoelectric sensors [48,49].

1.2. Subsystems of the Physical Sensors

The general structure of the physical sensors including four subsystems is shown in Figure 3.

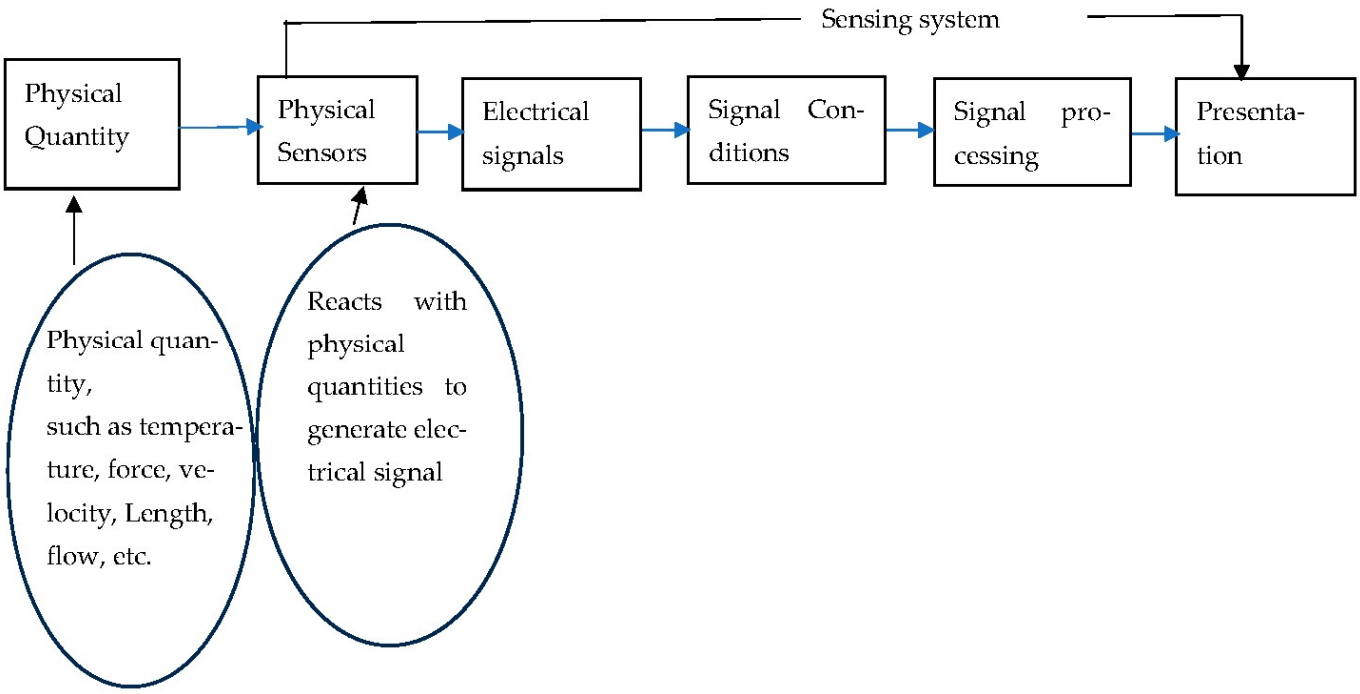


Figure 3. The general structure of physical sensors.

1. Sensing element

This element reacts to the measured object, and the change signals of the reaction include voltage, resistance, pressure, light energy, etc. [50]. For example, the thermocouple reacts to temperature and produces a microvolt, and the strain gauge reacts to mechanical stress by changing its resistance. Thermistors or PT-100s react to temperature changes by varying their resistance [51].

2. Signal conditioning element

The response signal generated by the sensing element is processed into a signal that is easy to process, such as voltage, current, or frequency [52]. A typical signal conditioning element features an amplifier that amplifies the microvolt signal to a voltage level suitable for further processing. The Wheatstone bridge converts resistance into voltage, and a frequency-to-voltage converter changes the frequency into voltage [53].

3. Signal processing element

The signal of the above signal conditioning element is converted into a signal suitable for presentation [54]. This subsystem has hardware, such as an analog-to-digital converter (ADC), which converts voltage into digital signals, and software, which converts digital signals into measurement values through calibration equations or calculates signals from different components into new measurement signals, such as flow data and air density data into mass changes per unit time [55,56].

4. Data presentation element

The signals mentioned above can be presented using liquid crystal display (LCD) or transmitted via digital signals combined with modern communication technology and the Internet [57,58].

1.3. The Characteristics of the Physical Sensor

From the four subsystems of the above measurement system, we can determine the characteristics of the physical sensor.

1. Versatility and standardization

The versatility of the hardware is evident in its signal conditioning, signal processing, and data presentation capabilities [59]. For example, the Wheatstone bridge, used to convert resistance into voltage, can be applied to all sensing elements that convert resistance into voltage, such as thermistors, PT-100, and strain gauges. The signal processing element's ADC and DAC (digital-to-analog converter) can be used interchangeably [60]. Data presentation elements, such as LCD, Bluetooth, ZigBee, and other devices, are compatible. These components have also been standardized in the industry [61].

2. The physical sensing element has good repeatability [62–64]

For example, thousands of PT-100 (platinum resistance detectors) all have a resistance characteristic of 100 ohms. For thermocouple wires, if we randomly sample five 2 m wires from a 10,000 m long thermocouple wire, the relationship between voltage and temperature is almost the same for the five wires [64].

3. Each sensing element has its specific calibration equation.

The signal processing element has calculation software that converts the response value into a measurement value [65,66].

For example, temperature measurement has different specifications of thermocouples, resistance temperature detectors (RTDs), and thermistors. A relationship equation has been established between the output signal of each component (in microvolts or resistance) and the measured temperature [67].

4. Establishment of the calibration equation

Physical measurements can be calibrated using their SI base units [68]. The seven basic units of SI are time, length, mass, electric current, temperature, amount of substance, and luminous intensity. SI-derived units are then established based on these seven basic quantities. For example, speed measures distance over time [69].

Taking temperature as an example, the triple points of different substances are used to establish the temperature reference point. Then, based on this, a temperature calibrator is made to provide calibration operations for commercial thermometers [70].

The standard basis for this calibration equation includes the standard environment (temperature, relative humidity, etc.) [65,71] and the standard material (standard length, standard weight, etc.) [72].

Different standard systems are based on different required performance. For example, the relative humidity calibration environment includes the two-pressure, two-temperature, two-flow, and saturated salt solutions [73].

5. Impact of the working environment

During measurement operations, factors such as the ambient temperature, electromagnetic waves, and applied voltage often cause interference in the measurement signal. The physical sensor has already processed or compensated for these issues [74].

When the sensor is measuring, its output signal changes with the measurement time, and only after some time does its measurement signal become stable [75]. Physical sensors use mathematical models to resolve this time-delayed dynamic signal problem [76].

Measurement Theories for Physical Sensing

Because the physical sensors are the foundation of industry, academia has established a complete set of measurement theories for physical sensing, such as [77,78]:

1. Distinguishing between accuracy and precision and expressing them in terms of the mean and standard deviation [79,80].
2. Establishing basic concepts of standard materials and standard environment. Therefore, an error value can be defined. The error is the difference between the average value of multiple measurements and the standard value [81,82].
3. Standard materials and standard environments are traceable, and seven benchmark quantities, including length, mass, time, temperature, electrical quantity, mole, and illumination, are established. The accuracy of standard quantities at different levels is then established based on these benchmark quantities [83,84].
4. Establishing the concept of uncertainty. The sensor's performance can be incorporated into the concept of statistical variability [47,85,86].

The schematic of the measurement theories is given in Figure 4.

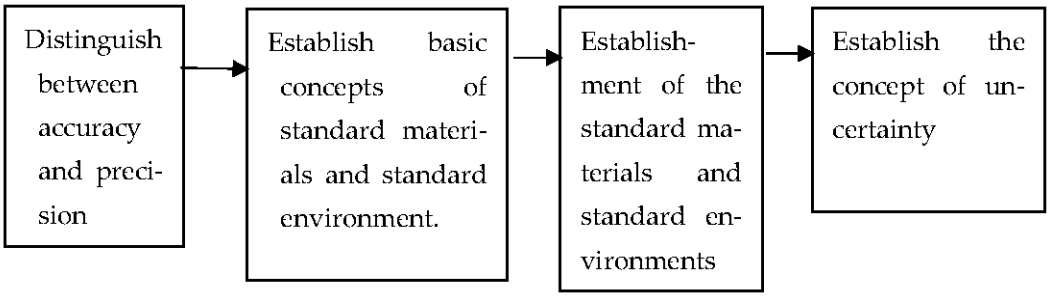


Figure 4. Schematic of the measurement theories.

1.4. Chemical Sensors

Richard and Climensa [87] describe the definition of chemical sensors. Chemical sensors use a specific material as the sensing element to interact with the target analyte. The interaction between sensing elements involves changes in electrical properties, the emission of light, the accumulation of mass on the sensing element, and heat reactions, among others. These changes are then translated into electrical signals for further processing [4–7,15].

The general structure of the chemical sensors is given in Figure 5.

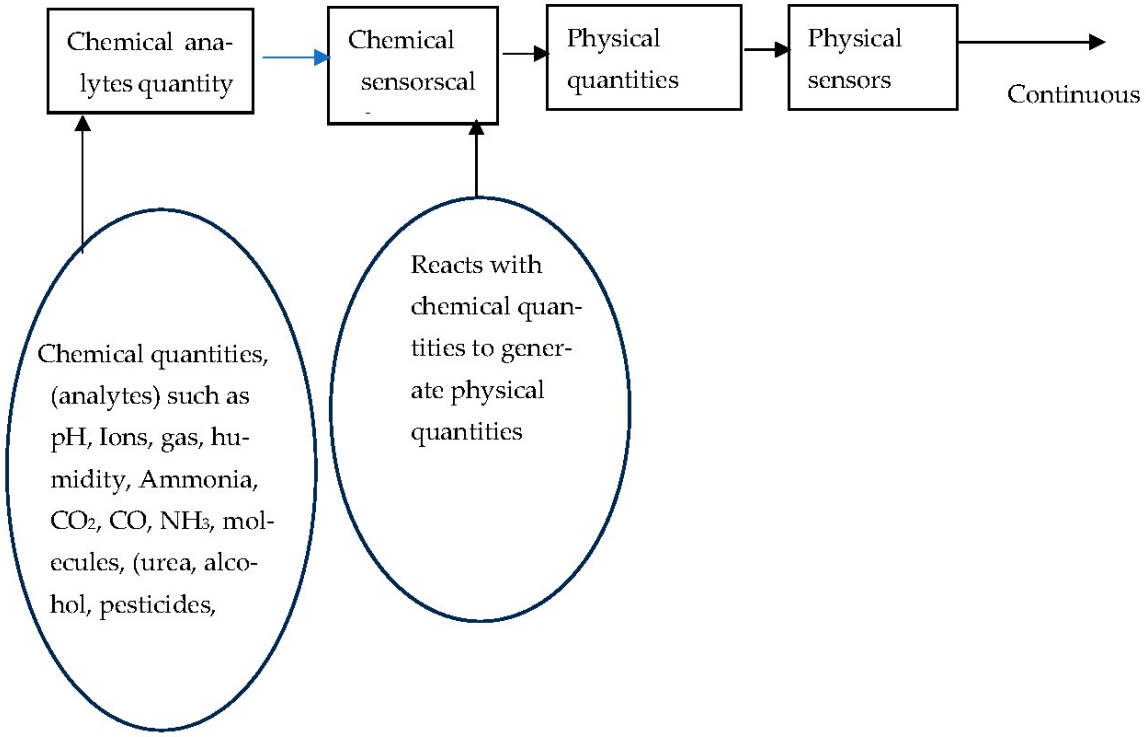


Figure 5. General structure of the chemical sensors.

The chemical sensors measure the gas concentration, chemical composition, ion concentration, and reaction rate, among other parameters [4,6,7,9]. The gas sensors are used as examples and introduced as follows:

The crystal lattice of a semiconducting oxide is used to detect the O_2 concentrations. At very high temperatures (>700 °C), the adsorption of O_2 molecules, which involves extracting electrons from the metal oxide, reduces conductivity. By measuring the resistive variation, the O_2 in the air can be detected [87,88]. The concentrations of other gases can be measured by observing the change in resistance of other metal oxides. The conductive polymer gas sensors can absorb gas vapor and increase their resistance. These sensors can work in ambient air. The response of both chemical sensors is characterized by a change in resistance [87,88].

The selective binding agent can utilize surface acoustic wave (SAW) sensors to measure gas concentrations, such as HCl, H_2, H_2S, NH_3, and SO_2, in a film deposited on the crystal surface [89]. The adsorption of gas affects the wave speed of this sensor. The response of this chemical sensor is characterized by a change in speed [90,91].

The predetermination calibration equations can calculate the gas concentrations by measuring the changes in resistance or the speed of the sensors.

Four primary transducers, including electrochemical, optical, mass, and thermal transducers, are designed to convert the response of chemical sensors into an electrical signal, allowing for conditioning and processing [92].

Electrochemical sensors detect all electrical changes (voltage, current) from these chemical interactions. The calibration equations are essential for their performance [93–95].

Optical sensors detect changes in light properties, including absorption, reflection, fluorescence, and light scattering [96,97].

Mass sensors are used to detect changes in mass. Due to its sensitivity to tiny mass changes, the quartz crystal microbalance (QCM) is the typical transducer used for mass change [98,99].

Thermal sensors measure temperature changes resulting from chemical reactions. The rapid response of sensors ensures their performance [100,101].

The responses of these four chemical transducers must be detected and processed by the physical sensors. So, the research and development of chemical sensors is based on the foundation of physical sensors.

The essential characteristics of chemical sensors are introduced as follows:

1. Frequent calibration

This is critical to ensuring the performance of chemical sensors. The influencing factors include the environment, aging, contention, and others. For measurement, it is necessary to calibrate these sensors [102]. Standard or reference materials are beneficial for maintaining the validity of sensors [103].

2. The recovery time

Before the subsequent measurement, chemical sensors require time to recover their performance [104,105].

3. Dynamic time of response

Chemical sensors typically require a period to reach a stable state; the time to achieve equilibrium is usually longer than that of physical sensors [106,107].

4. Cross-sensitivity

When the chemical sensors used to detect a specific chemical component are present in an environment with multiple substances, some substances have a chemical reaction with the sensing element. The signals from other substances will interface with the target substances' signals [108–110].

5. The trends of chemical sensors

These include faster response times, miniaturization, and more sensitive integration with the Internet of Things (IOT) [87].

The development of physical sensors has significantly influenced the advancement of chemical sensors, leading to numerous significant breakthroughs in recent years. In terms of the sensing elements, many novel chemical materials have been developed. These materials have better single selectivity and environmental resistance [111].

Significant improvements have also been made in the various options for membranes, components, and ways of connecting signal processing subsystems [112].

Optical sensors based on the principle of spectroscopy can better combine optical principles. Electrochemistry, which is based on voltage and current measurement, also introduces newly developed electrical principles [113].

Chemical sensors researchers have widely accepted the establishment of chemical reference materials and are gradually moving towards standardization and internationalization [114,115].

Measurement uncertainty calculation is recognized as a basic requirement for chemical sensors [116]. The most significant limitation in developing chemical sensors is the presence of multiple components and non-uniform distribution in the measured object.

1.5. Reference Materials

Certified reference materials (CRMs) are used for traceability, to validate analytical measurement methods, or as a "control" or standard for instrument calibration. This certified reference material is a special measurement standard [117,118].

Analytical instruments or sensors require reference materials of known composition for accurate calibration. This reference material is produced under strict manufacturing procedures and can be certified. The reference data provided are traceable [119,120].

The standard materials used in chemical sensing calibration can be divided into two categories: pure standard materials and matrix standard materials [83,84,121]. Pure standard substances are extremely high-purity substances. Matrix standard substances are slightly permeated into standard gases or standard solutions prepared by diluting high-purity substances [121]. Common standard solutions include pH standard solutions, inorganic standard solutions, and organic standard solutions. Inorganic standard solutions are made by dissolving high-purity reagents in water or acid [83,84]. Organic standard solutions are prepared by dissolving the reagents in organic solvents. Certified reference materials provide the highest accuracy, uncertainty, and traceability in SI measurement units [122].

Reference materials are one level below the certified reference material. They must be provided by a certified reference material manufacturer [123]. Reference materials are not as accurate as certified reference materials but are easier to produce and still meet ISO requirements. Where traceability requirements are less stringent, this can provide a lower-cost solution than certified reference materials [124].

Commonly used standard substances for the calibration of chemical instruments and sensors include pH buffers, EC standards, total suspended solids (TSS) standard, biological oxygen demand (BOD) standards, chemical oxygen demand standards (COD), total organic carbon (TOC) standards [123–125] and trace elements [126].

1.6. Biosensors

A biosensor is a device that utilizes biological materials as the sensing element to measure reactions and generate signals in response to the concentration of the analyte in these reactions [3–5].

The special characteristic of biosensors is the high selectivity of biological reactions. Biological substances are used as sensing elements, including antibodies, DNA probes, glucose, enzymes, live cells, and microorganisms [3–5,7,9,10].

The general structure of the biosensors is given in Figure 6.

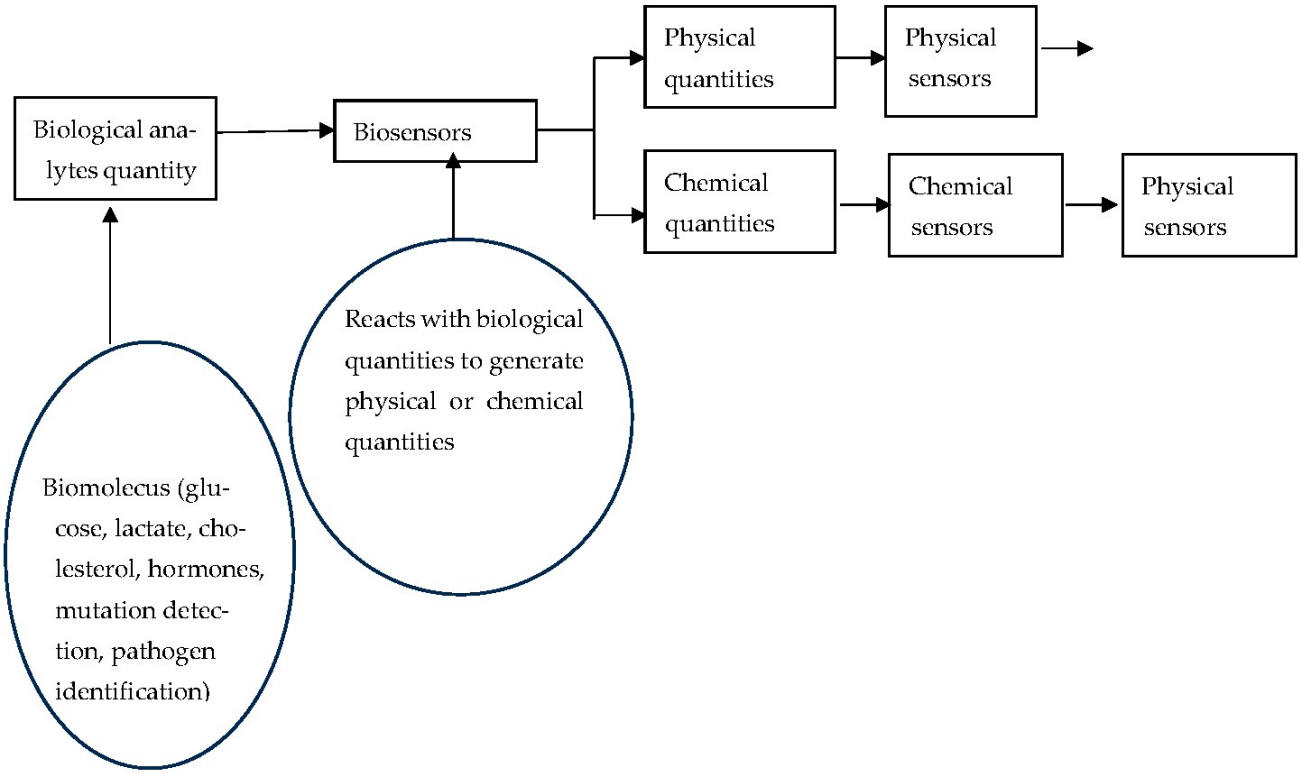


Figure 6. The general structure of the biosensors.

For biosensors, there are two methods used to detect the response of biological elements.

If the response of biosensors is in the form of electrical, optical, mass, and thermal signals, they can be processed using the four primary transducers, similar to chemical sensors [4,6,7,9]. This is called direct signal processing. The physical sensors detect the responses of these biosensors [127,128].

If we assume that the response of the biosensors is chemical signals, such as the change in pH, gas concentrations, EC, etc., these four primary transducers cannot be used to process these signals directly [3–5,129]. Chemical sensors must be used to detect these signals. These biosensors comprise biosensing materials, chemical sensors, and physical transducers. This is referred to as indirect signal processing [9,10,13,130].

Some typical biosensors are introduced for a urea biosensor based on an ENFET (enzyme field-effect transistor), where urease serves as the sensing element in the sensing gate, and changes in urea concentration alter the pH values. The pH value is determined by a pH meter [4,7]. For a uric acid biosensor, the urease enzyme is the sensing element. The reaction with uric acid in the uricase produces O_2. Then, a dissolved oxygen sensor developed based on chemical sensing principles is used to detect the O_2 concentration. In other words, a chemical sensor is used to detect the response of these biosensors [131,132].

Suppose a biosensor interacts with the substance being measured. In that case, the resulting reaction can only be measured using expensive and complex instruments, and there are no existing physical or chemical sensors that can measure it. In this case, commercializing such biosensors will be difficult.

Currently, two types of commercial biosensors are widely available on the market [133].

The first type of biosensor is the glucose meter. It detects glucose concentrations in blood and displays the measurand in numerical values.

The second biosensor type is the paper-based biosensor, which includes pregnancy test sensors and COVID-19 rapid antigen test strips [23]. Pregnancy sensors use a lateral flow immunoassay to detect the hormone HCG in urine. It reveals the color change and is detected by human vision. The results are positive or negative [24,134].

The COVID-19 rapid antigen self-test nasal contains lateral flow assays using antibodies to detect viral proteins of the virus. The result is the color change observed by vision. Sometimes, the change in color is used to justify the quantity of the virus [134].

The comparison of the physical, chemical, and biosensors is listed in Table 2.

Table 2. Comparison of the physical, chemical, and biosensors.

Aspect	Physical Sensors	Chemical Sensors	Biosensors
Sensing Element	Physical phenomena (e.g., temperature, pressure, acceleration)	Chemical-sensitive materials (e.g., metal oxides, polymers, SAW films)	Biological elements (e.g., enzymes, antibodies, cells, DNA)
Detection Principle	Electrical or mechanical response to physical change	changes in electrical properties, the emission of light, the accumulation of mass on the sensing element, and heat reactions, due to chemical interactions	Biochemical reactions leading to physical or chemical signal generation
Signal Processing	Direct (ADC, DAC, amplifiers, display interfaces)	Direct (resistance, current, wave speed); often needs calibration	Direct (processed via transducers) or indirect (requires chemical/physical transducers)

Table 2. *Cont.*

Aspect	Physical Sensors	Chemical Sensors	Biosensors
Typical Applications	Temperature, pressure, displacement, humidity, acceleration	Gas sensing, pH, ion concentration, chemical composition	Medical diagnostics, food safety, environmental monitoring, personalized healthcare
Key Features	High detection limits Cross-reactivity in complex matrices Inadequate specificity in real samples	- Specific to certain chemicals - Requires frequent calibration - Sensitive to the environment. - Can exhibit cross-sensitivity - Integration with IoT trending	- Highly selective due to biological specificity - Can detect trace biological substances - Interface with chemical/physical sensors - Require biological immobilization
Interference and Cross-Sensitivity	Generally well-compensated in design (EM interference, temperature)	Significant issue; can be affected by non-target analytes	High selectivity, but can be influenced by complex sample matrices (e.g., blood, food)
Standardization	High, well-defined standards, protocols, materials	Increasing reference materials and protocols are emerging	Low; immobilization methods and biological stability hinder standardization
Trends and Advances	Enhanced miniaturization, wireless integration	Improved materials, sensitivity, selectivity, and IoT integration	Focus on stability, reproducibility, scalability, and practical usability
Commercialization Status	Widely used and mature in the industry	Mature in some applications (e.g., gas sensors), still advancing	Mostly in research/prototype stage; few widely commercialized examples (e.g., glucose meters, pregnancy tests)

2. The Characteristics of the Glucose Meter

2.1. The History of the Glucose Biosensors

The first generation of glucose sensors uses glucose oxidase (GOx) to catalyze glucose to gluconolactone, which is then hydrolyzed to gluconic acid. This process produces hydrogen peroxide (H_2O_2) [135,136]. The H_2O_2 is then oxidized at a platinum or carbon electrode, generating an electrical signal proportional to the glucose concentration. This method can be used to obtain the glucose concentration through a calibration equation by measuring the electrical signals generated by the biochemical reaction [137,138]. This method relies on an ambient oxygen supply. Other substances may also interfere with the measurement performance [135–139].

The second generation of sensors uses media such as hexacyanoferrate, benzoquinone, ferrocene and its derivatives, methylene blue, and phenazine methyl sulfate to enhance electron transfer, reduce dependence on oxygen, and enable the stability of signals [140,141].

In the manual "Glucose Meter Fundamentals and Design" [142,143], the development of a glucose sensor is introduced in detail. The glucose oxidase enzyme serves as the sensing element. The glucose in blood is oxidized with oxygen, which causes a decrease in oxygen and an increase in hydrogen peroxide. The test strip measures the electrical current due to the reaction that represents the glucose concentration. Three electrodes are installed in the test strip terminals: trigger (counter), working, and references [142,143].

The reading device for the test strips included a current-to-voltage converter, an amplification and filtering circuit, several reference voltage generators, and the software model in a communication device [137,138]. The electrical industry supplies these devices, which are typically used in industrial settings, but they are not explicitly designed for glucose meters.

2.2. Characteristics of Glucosidases for Glucose Biosensors

Glucosidases are a group of enzymes that hydrolyze glycosidic bonds in carbohydrates, releasing glucose or other sugars. These enzymes have significant potential for biosensor development, particularly for glucose meters used in diabetes monitoring [44,136,139,144,145]. The characteristics that make them suitable as biosensing elements are:

1. Catalytic activity

The glucose released by the enzymatic reaction can be quantitatively measured, providing a basis for glucose sensing [146].

2. Specificity

These enzymes typically act with high specificity, minimizing interference from other sugars or compounds in biological samples and improving the accuracy of glucose measurements [147,148].

3. Stability

Glucosidases maintain their activity over a wide range of temperatures and pH levels [149].

4. Enzyme immobilization capability

Glucosidases can be immobilized on sensor surfaces (e.g., electrodes, membranes) without significant activity loss [149].

5. Enzyme kinetics

Glucosidases often exhibit rapid catalytic turnover, resulting in the rapid generation of signals [149].

6. Coupling with transduction mechanisms

The glucose released by glucosidase activity can be detected using electrochemical methods, especially amperometry [150].

7. Signal amplification

Integration with redox mediators or nanoparticles can enhance signal strength and sensitivity [149].

8. Biocompatibility and safety

Glycosidases are biocompatible and safe for use in wearable or implantable glucose sensors [151].

2.3. The Control Solutions of Glucose Biosensors

The performance of the glucose biosensors is validated with the commercialized glucose control solution [152].

The glucose control solution is a reference material. It is a liquid made up of pure water, glucose, buffer, and microbicide. This control solution provides a standard glucose concentration for testing the performance of blood glucose meters and test strips. Its pH value is close to the physiological pH value of human blood. Having a microbial inhibitor prevents the growth of microorganisms, thereby preventing changes in glucose

concentration due to the presence of microorganisms [153]. Calibrating a blood glucose meter, especially in continuous glucose monitoring (CGM) systems, uses a control solution to ensure accurate readings [154]. This process is easy to use and typically includes using a control solution, inserting a test strip, and comparing the meter reading with the control solution value [155].

2.4. Success Factors of Blood Glucose Meters

The commercialization of blood glucose meters has been successful because they are technologically mature, inexpensive, easy to use, and can serve users with critical, ongoing healthcare needs [3,136–139]. Diabetes is a chronic disease that is widespread, long-term, and not immediately fatal. Patients can effectively control this chronic disease by measuring their blood sugar, making it the world's most widely adopted and commercially viable biosensor [3,156–161]. Blood glucose meters are considered the most successful biosensors on the market for several reasons:

2.4.1. Technical Aspects

1. Mature technology

Blood glucose meters have been developed over the decades and are reliable and accurate.

Their accuracy and repeatability meet the relevant requirements, and they have long-term stability [136,137,157,158,162,163].

2. Accessibility of sensing elements

The sensing element, glucose oxidase enzyme, is a commonly used raw material in food and other industries. It has high stability, high purity, and sophisticated refining technology. The material is stable and easy to store. Compared with other enzymes, the cost is low [138,156,158].

3. Availability of the standard reference materials

Glucose standard reference materials have been developed. They are popular as commercial control solutions daily, without requiring expensive certified reference materials. They are provided as control solutions to calibrate blood glucose meters to ensure accuracy; see [136,138,160].

4. Easy to use

The blood glucose meter is small, portable, and easy to use. Typically, only a drop of blood is required to provide results within seconds [136,137,139,156–160,163].

5. Continuous innovative development.

With the integration of digital health management, many blood glucose meters sync with smartphones and health apps to enable better data tracking and disease management [137–139,157].

6. Development of continuous glucose monitors (CGM).

The field of blood glucose measurement continues to advance as a new generation of biosensors provide real-time tracking [161–163].

2.4.2. Larger Market

The following reasons make glucose biosensors a large market.

1. Huge demand

Diabetic patients must monitor their blood sugar levels continuously throughout the day. Hundreds of millions of people worldwide have diabetes. Diabetes has become prevalent in emerging countries such as China, as well as nations in Southeast Asia, Eastern Europe, and North Africa. The market demand for blood glucose meters is enormous and continues to grow [164–168].

2. The characteristics of diabetes

Diabetes is a chronic disease, i.e., not a disease that causes immediate death. Long-term treatment is required. Blood glucose monitoring is essential in managing type 1 and type 2 diabetes and requires several daily measurements [165,166,168,169].

3. Strict blood sugar control

Continuous blood sugar monitoring enables patients to maintain their blood sugar levels within a safe range. Strict blood sugar monitoring can reduce the risk of neuropathy and avoid serious complications such as blindness or cardiovascular disease [165–167,169].

4. Controlled insulin dosage

Real-time blood glucose readings are essential for determining the insulin dosage for patients [165,167–169].

2.4.3. Institutional Aspects

1. Regulatory approval and standardization

Blood glucose meters already have a sound regulatory system. Equipment must meet strict standards (such as those set by the FDA and ISO) before it can be sold, thereby enhancing product credibility and reliability [170,171].

2. Reimbursement of purchase funds

This can usually be covered by insurance or public health systems, reducing the financial burden on users [172,173].

2.4.4. Financial Aspects

The commercial success of these biosensors can contribute to the massive revenue generated by the blood glucose test strips and sensors market, creating continuous income for manufacturers, so they invest more resources in continuous research and development [174].

3. Highly Developed and Competitive Biosensors

There are two types of highly developed and competitive biosensors: continuous glucose monitoring (CGM) and paper-based biosensors.

3.1. Continuous Glucose Monitoring (CGM)

Continuous glucose monitoring (CGM) measures a user's continuous blood sugar levels, allowing them to adjust their diet and lifestyle in real-time according to their insulin dosage to control their blood sugar more effectively [175–183].

Continuous glucose monitoring (CGM) is a device that continuously tracks blood sugar levels in the body. Instead of relying on occasional finger stick blood tests, CGM systems provide real-time blood sugar data by measuring glucose in interstitial fluid (the fluid surrounding cells). This enables individuals with diabetes to track their blood sugar trends. Early detection of rising or falling blood sugar can help users take timely measures to prevent serious complications such as hypoglycemia or hyperglycemia. Therefore, CGM can also help medical staff make more informed decisions about adjusting treatment plans [177,179,181,182].

CGM systems comprise three main components: sensors, transmitters, and receivers or display devices [179–182]. Sensors are small, flexible wires inserted under the skin that measure blood sugar levels in interstitial fluid. The transmitter connects to the sensor and sends blood sugar readings wirelessly to a compatible display device. The receiver or display device can be a dedicated handheld device, a smartphone, or a smartwatch, used to display real-time blood sugar data, trends, and alerts [180,182,183].

The primary advantage of CGM is its ability to monitor blood glucose levels continuously, rather than intermittently. CGM also provides trend information, showing how quickly blood glucose is rising or falling, which can improve overall blood glucose control and reduce dangerously high or low blood glucose values. Another advantage is early warning, which can notify users before their blood glucose levels reach critical levels, allowing for proactive treatment. CGM can also reduce the frequency of fingerstick blood tests, improving user comfort and quality of life. Data collected over a long period can help users and healthcare providers understand blood glucose patterns, enabling them to make informed decisions about diet, exercise, and medication adjustments [180–182].

CGM systems do have some limitations and challenges. The primary concern is the accuracy of blood glucose readings. Glucose measurements in interstitial fluid often lag behind blood glucose measurements by several minutes [183]. This can impact decisions when blood glucose levels change rapidly. Some sensor models may still need calibration [184,185]. Cost remains a barrier to CGM use for many patients, especially in areas without medical coverage. Continuous wearing of sensors may cause skin irritation or discomfort for some users. Issues such as sensor aging, signal loss, or data transmission delays also affect reliability [184,185].

The trends and future implications of continuous glucose monitoring (CGM) are listed in Table 3.

Table 3. Trends and future implications of continuous glucose monitoring (CGM).

Trend	Description	Future Implications
1. Transition to non-invasive and minimally invasive technologies [181,186]	Development of CGMs using interstitial fluid, sweat, saliva, or optical signals rather than subcutaneous sensors.	Increased patient comfort, improved compliance, and broader use among prediabetic individuals and health-conscious populations.
2. Miniaturization and skin-adherent technologies [187,188]	The inner, smaller, flexible sensors with skin-like properties are being developed.	Improved wearability, particularly for children and active users, with potential applications in consumer wellness wearables.
3. Real-time data analytics and alerts [189,190]	Advanced CGMs offer continuous, real-time glucose readings and trend analysis with predictive alerts.	Early intervention for hypo- and hyperglycemia; enhanced safety during sleep, exercise, or illness; improved decision support for users and clinicians.
4. Smartphone and wearable integration [191,192]	CGM devices sync with smartphones, smartwatches, and fitness trackers for data visualization and sharing.	A provides a more user-friendly experience, enhanced remote monitoring by caregivers and healthcare providers, and integration into digital health ecosystems.
5. Data sharing and cloud connectivity [193,194]	CGM platforms enable cloud storage, data sharing, and AI-based analytics.	Personalized treatment strategies, improved telemedicine services, and population-level diabetes management insights
6. AI and predictive modeling integration [195,196]	Use of machine learning to predict glucose trends and recommend actions.	Precision medicine for diabetes management: potential to extend predictive analytics to comorbidities and lifestyle patterns.
7. Extended sensor lifespan and calibration-free devices [197–199]	New CGMs are now factory calibrated and can function continuously for 10–14 days or longer.	Reduced user burden and maintenance; broader acceptance among users who previously resisted CGMs due to inconvenience.

3.2. Paper-Based Biosensors

Paper-based biosensors are a promising, convenient, and cost-effective diagnostic tool, particularly in resource-constrained settings. They are simple to operate, inexpensive, and fast [200–205].

A paper-based biosensor is an analytical device that detects biomolecules using a simple, low-cost paper platform. The primary function is to identify the presence or concentration of a specific analyte (e.g., glucose, pathogens, toxins, or biomarkers) through a biochemical reaction. Such biosensors are particularly suitable for point-of-care diagnostics, environmental monitoring, food safety, and resource-constrained settings where traditional laboratory equipment is unavailable [200–204].

The structure of a paper-based biosensor comprises three basic components: a paper substrate, a biorecognition element, and a transduction system. The paper substrate acts as both a support and a fluid transport medium, allowing the sample to flow via capillary action without the need for an external pump [201,202,206]. The biorecognition element (e.g., enzyme, antibody, or nucleic acid) is immobilized on specific areas of the paper substrate and selectively interacts with the target analyte. These interactions generate signals that are then converted into output signals by the sensing system. The output signal can be a color change, an electrochemical signal, or a fluorescent signal. Some paper-based biosensors are designed for lateral flow analysis (e.g., pregnancy tests). Others use origami-like folding designs or microfluidic channels for multiplexed analysis [203,204,206].

Paper-based biosensors have many advantages. They are inexpensive, as paper is a readily available and biodegradable material. They are portable and lightweight, making them ideal for use in remote or resource-poor areas. Because capillaries drive fluid movement, these biosensors typically do not require an external power source [202,207]. They are easy to use and often provide visual results, making them accessible even to non-expert users. They support rapid detection and can be mass-produced using relatively simple manufacturing techniques such as printing or wax models. Their flexibility and adaptability also allow them to be integrated with smartphones or wearable devices for enhanced digital readout and data sharing [202,206,207].

Despite their many advantages, paper-based biosensors also face many challenges [208–210]. The main limitation is that their sensitivity and accuracy may be lower than those of traditional laboratory detection methods. The limited sample volume and the porous nature of paper can affect the consistency of results, making quantitative measurements difficult. Environmental conditions, including temperature, humidity, and storage stability, can also affect performance and reliability. Integrating multifunctional detection systems into paper-based platforms remains a technically challenging task [208,209]. Scalability, standardization, commercialization, and obtaining regulatory approval remain hurdles to overcome [209,210].

The trends and future implications of paper-based biosensors (PBBs) are listed in Table 4.

Table 4. Trends and future implications of paper-based biosensors (PBBs).

Trend	Description	Future Implications
1. Low-cost and disposable designs [211,212]	Increasing use of inexpensive materials (e.g., cellulose paper) and simple fabrication methods (e.g., wax printing).	Widely accessible diagnostics in low-resource and rural settings; scalable production for large-scale use in pandemics and screening programs.
2. Integration with microfluidics [213,214]	Development of microfluidic paper-based analytical devices (μPADs) for fluid handling, mixing, and multiplex testing.	More complex, multi-analyte detection in a single test strip; applications in environmental, food, and clinical testing.

Table 4. *Cont.*

Trend	Description	Future Implications
3. Use of nanomaterials and advanced functional inks [215,216]	Incorporation of nanoparticles (e.g., gold, carbon, graphene) to enhance sensitivity and specificity.	Improved performance rivals that of traditional biosensors, with potential for early disease detection and analysis of ultra-low concentrations.
4. Digital and smartphone-based readout systems [217,218]	Coupling with smartphones for data acquisition, image analysis, cloud connectivity, and even result interpretation using AI.	Making healthcare diagnostics accessible and interpretable by non-experts; enables telemedicine and remote health monitoring; and provides real-time data tracking for epidemiology and personalized medicine.
5. Eco-friendly and sustainable development [219,220]	Emphasis on biodegradable materials and greener manufacturing processes.	Reduced environmental impact of disposable diagnostics; aligns with global sustainability goals.
6. Environmental and food safety monitoring [221,222]	Expanding application from medical diagnostics to detecting pesticides, heavy metals, or pathogens in food/water.	Preventive public health strategies and rapid screening tools for agricultural and environmental surveillance.
7. Personalized and home-based testing [218,223]	Movement toward user-friendly, at-home test kits for chronic disease management and infectious disease screening.	Empowerment of individuals in health monitoring; potential to reduce the burden on healthcare systems
8. Mass production and commercialization [210,224]	Scalable manufacturing techniques like screen printing, inkjet printing, and laser cutting—standardization efforts for regulatory approval and industrial adoption.	Leads to wider market availability and lower per-unit cost; Drives competition and innovation among medical device startups and established companies.

4. Challenges in the Development of Biosensors

4.1. Issues in the Commercialization of Biosensors

The non-technical and regulatory aspects of developing biosensors include the gap between academic researchers and industry connections, the protection of intellectual property, and the stringent approval processes of the medical equipment. However, these are ordinary problems in the research related to medical equipment [225].

The specific issues in the commercialization of biosensors are as follows:

4.1.1. Completeness of Scientific Development

1. Stability and shelf life: many biosensors use biological components (enzymes, antibodies, etc.) that degrade over time, making them less suitable for mass production or long-term storage. Many prototypes fail to meet this requirement [226,227].
2. Selectivity and sensitivity: interference from other substances can reduce sensor accuracy in real-world samples, such as blood or food [228,229].
3. Reproducibility: many biosensors developed in laboratories operate under controlled conditions, but reproducing consistent performance in real-world settings is significantly more challenging [230]. Ensuring that every sensor behaves the same way under the same conditions is difficult, particularly for biosensors that rely on biological components [231].

4.1.2. Oversimplifying the Practical Application

Regarding research methods, a common problem is that the research is oversimplified and far from the actual situation [232,233]. For example, in the research on sensing antibiotic residues in pork, the researchers directly measured the antibiotic concentration in pig blood serum using electrical voltammetry [234,235]. The original target of this research was the concentration of antibiotics in pork. However, the measurement object during the research was pig blood serum. The two objects differ significantly in terms of their structural composition and the uniformity of antibiotic distribution [234,235].

4.1.3. Challenges of Mass Production

1. Scalability: laboratory biosensors might work well in research, but scaling them for consistent mass production can be expensive and technically demanding [236].
2. Cost of materials: high-quality biological recognition elements (e.g., monoclonal antibodies) can be expensive or difficult to produce in large quantities [237].
3. Complex fabrication: some biosensors require intricate nanomaterials or microfabrication methods that are hard to scale cost-effectively [238,239].
4. Batch-to-batch variability: maintaining quality across mass production is a hurdle [239].

4.1.4. Market Demand and Development Costs [236]

1. High development costs: from prototype development to market-ready product, costs can skyrocket, especially with the need for specialized equipment, materials, and expertise [240,241].
2. Low return on investment: the market may be too small for specific niche applications to justify commercialization [242].
3. Limited market: some biosensors address niche problems or lack sufficient demand to justify full commercialization [243].

4.2. The Methods of Immobilization

The importance of immobilization lies in maintaining biological activity, stability, and shelf life. It prevents the release of biomolecules and enhances thermal and chemical stability.

Immobilization methods are crucial for the development of biosensors, as they directly affect the performance, stability, sensitivity, and reliability of the sensor [244–246]. For commercial or field applications, biosensors must remain stable over time and under different conditions (pH, temperature, storage). The orientation, density, and accessibility of the immobilized molecules affect their efficiency in interacting with the target and generating a detectable signal [245,246]. Standardized and controlled immobilization methods ensure that each biosensor performs the same. The method selected must be able to support efficient signal transmission and be compatible with the sensor surface. Choosing the proper immobilization method requires a balance between maintaining biological activity and achieving mechanical, chemical, and operational robustness [247,248].

Several methods for connecting the sensing elements to the transducer are listed below [4,244]: (1) adsorption onto a surface, (2) microencapsulation, (3) entrapment, (4) covalent attachment, and (5) cross-linking. The advantages and disadvantages of the five methods of immobilization are listed in Table 3. The effectiveness of the immobilization is critical to maintaining the functionality of the biosensor [245,246].

There is no perfect immobilization method for biosensors because each method involves trade-offs among several critical factors, and no single approach can simultaneously satisfy all the desired characteristics.

Different methods directly impact the performance of biosensors, including sensitivity, selectivity, response time, and lifetime. Each method has its advantages and disadvantages. Combining two or more methods to optimize performance is sometimes necessary in practical applications [245–249].

A typical example is the effective attachment of glucose enzymes to the transducer surface used in blood glucose sensing.

4.3. Market Competitors

Competition from existing technologies is a significant concern. If other diagnostic tools are already well-established, a biosensor might not be attractive despite its technical

advantages [250–253]. For example, the competitors of medical biosensors include medical instruments, such as the Automated Clinical Chemistry Analyzer [254].

An automated clinical chemistry analyzer is a laboratory instrument used in medical institutions. It is primarily used for the automatic measurement and analysis of the chemical composition of blood, urine, and other bodily fluid samples. Analyzers are commonly used in clinical laboratories to diagnose and monitor disease [255].

The primary function of the fully automatic blood biochemical analyzer is to perform biochemical analysis on blood samples in an automated manner and detect various biochemical indicators. For example, glucose is used for diabetes monitoring and electrolytes (e.g., sodium, potassium, chloride), for hydration and kidney function, liver enzymes (ALT, AST, ALP), for liver health, kidney markers (urea, creatinine), for kidney function, lipids (cholesterol, triglycerides), for heart disease risk, proteins (albumin, total protein), and for kidney function and liver condition, among others.

The automatic clinical chemistry analyzer features include automated testing, multiple test capabilities, high efficiency, accuracy, automatic report generation and data storage, and a low operational cost [256–259].

Considering the cost, the automatic clinical chemistry analyzer has the following factors: the measurement time is short, the number of samples measured per day is large, and the cost for the user is relatively low [257–259].

The features that make biosensors superior to clinical chemistry analyzers include the use cases that can be utilized in real-time, point-of-care, and wearable monitoring, as well as in diverse use environments, e.g., the home, field, or wearable devices.

In cases where the rapid identification of infection is required but precise measurement data are not necessary, biosensors can outperform clinical chemistry analyzers in terms of speed and convenience.

The development of biosensors differs from that of clinical chemistry analyzers in hospitals. The performance characteristics of biosensors must be understood and differentiated from those of Clinical Chemistry Analyzers, rather than requiring them to replace them entirely.

5. Future Trends for Glucose Detection

Future trends in glucose detection are being shaped by the need for non-invasive, continuous, accurate, and user-friendly monitoring technologies, particularly for diabetes management and care. The key trends are listed as follows:

5.1. Non-Invasive and Minimally Invasive Methods [181,260,261]

To move away from finger-prick and implantable sensors, novel technologies include the use of optical sensing (e.g., near-infrared spectroscopy, Raman spectroscopy), the development of sweat, saliva, or tear-based biosensors, and the utilization of microneedles for interstitial fluid detection to improve comfort, enhance compliance, and expand the user base.

5.2. Integration with Wearable Devices [191,192,262,263]

Glucose sensors are being integrated into smartwatches, skin patches, and contact lenses. For example, some smartwatches attempt glucose estimation via optical sensors. These real-time health tracking systems are integrated into daily life.

5.3. Enhancement of Continuous Glucose Monitoring (CGM) [179,181,182,264]

There are attempts to develop calibration-free CGMs with refinements in accuracy, size, battery life, and wireless connectivity. The lifespan is extended, lasting several months and enabling more autonomous diabetes management.

5.4. Alternative Biofluids for Detection [187,188,265]

There are also attempt to develop non-invasive, multi-parameter health monitoring from blood to sweat, saliva, tears, and breath. These biosensors require the stability and reliability of sensors in various environments.

5.5. Remote Monitoring and Telehealth Integration [193,194,266]

Cloud-based platforms for data sharing with healthcare providers could provide real-time alerts, remote diagnostics, and consultations, as well as better clinical support and proactive management.

5.6. AI and Predictive Analytics [195,267]

This technique uses physiological models and machine learning to predict glucose trends and offer personalized advice. The lifestyle of patients is recommended based on glucose patterns, informed by intelligent decision making and risk reduction.

5.7. Sustainability and Accessibility [268]

There is a focus on low-cost, eco-friendly, and widely accessible glucose detection technologies: for example, the minimal e-waste from wearable devices.

6. Conclusions

The research and development of chemical sensors is based on the foundation of physical sensors. Similarly, the research and development of biosensors is based on the foundations of chemical and physical sensors. Therefore, one should understand the principles and development history of physical and chemical sensors when researching biosensors.

If the reaction between the biosensor and the object being measured can only be detected through expensive and complex instruments, and there are no readily available physical or chemical sensors for measurement, then commercializing such biosensors will be very difficult.

There are two types of commercially successful biosensors. One is a sensor that can provide data, such as a blood glucose meter. The other type provides a qualitative result, either positive or negative, for example, pregnancy test strips. Supposing that the purpose is to conduct research on biosensors or publish journal articles, there are numerous sensor elements, various options for immobilization, and multiple methods for miniaturizing sensor elements. Considering various factors, the research topics related to biosensors are endless. If one wants to develop commercially viable sensors, glucose biosensors could serve as a demonstration example.

Research on biosensors necessitates an understanding of the fundamental factors that influence sensor performance, including standard substances, calibration equations, and measurement uncertainty. Developing physical and chemical sensors could provide biosensors with practical experience.

Despite rapid advancements, current biosensors still face several significant challenges and limitations in both research and real-world applications. The significant challenges and limitations in both research and real-world applications for the future perspectives of biosensors' development and applications are as follows:

1. Short lifespan and stability

Many biosensors (for example, enzymatic ones) degrade over time. These enzymes and biological components are sensitive to pH, temperature, and humidity. They lose activity over time, limiting their shelf life and usability, which leads to frequent replacements, increased costs, and lower reliability.

2. Complex fabrication and calibration

Due to batch-to-batch variability, high precision is necessary in sensor manufacturing. The variability requires frequent calibration in specific sensors (e.g., glucose monitors), resulting in higher production costs and the potential for inconsistent results.

3. Invasiveness and user discomfort

Many biosensors (such as glucose monitors) still require blood samples or implantable devices. The result is pain or irritation and a severe reduction in user compliance. The non-invasive solutions (e.g., sweat, saliva, breath sensors) are an emerging need.

4. Biofouling and surface contamination

Biosensors' surfaces are easily clogged or contaminated by proteins and cells in biological fluids. This diminishes sensor function and induces false readings. Anti-fouling coatings and surface engineering are required.

5. Data interpretation and user interface

Raw measurement data can be complex or variable, making it challenging to make sensor output meaningful and user-friendly. Users may misinterpret results without clinical guidance, so better software with AI-based analysis is an emerging need.

6. High cost of materials and devices

Advanced biosensors (e.g., nanomaterial- or MEMS-based ones) with specialized materials or sophisticated fabrication techniques can be expensive to produce, which limits their scalability.

7. Environmental and storage constraints

Many biosensors are not stable under varying environmental conditions and are easily degraded in humid or hot climates. They need special equipment, such as a refrigerator for storage. They have limited use in field settings or low-resource areas.

8. Regulatory and Standardization Barriers

Biosensors must meet stringent regulatory approvals (e.g., the U.S. Food and Drug Administration (FDA)) before entering the market. This requires time-consuming and expensive trials. The lack of global standardization also slows commercialization and innovation.

The recommendations for future research related to biosensors, as discussed in the contents of this review, are as follows:

1. Enhance sensitivity and selectivity

Many biosensors still struggle with detecting low analyte concentrations in complex biological or environmental samples. Possible methods include the development of nanomaterials and the integration of molecularly imprinted polymers (MIPs) or aptamers to improve target specificity.

2. Advanced wearable and implantable biosensors

Real-time, continuous monitoring of health parameters is increasingly valuable for managing chronic disease with biosensors. Possible approaches include focusing on non-invasive or minimally invasive formats and enhancing the biocompatibility and long-term stability of materials.

3. Development of the environment-friendly paper-based biosensors

Low-cost, disposable sensors are critical for global health, environmental monitoring, and point-of-care diagnostics. They are discarded after use. The methods include the use of biodegradable substrates and environmentally friendly manufacturing processes.

4. Focus on global health and resource-limited regions

There is an urgent need for affordable diagnostics in underdeveloped and remote areas, and the development of biosensors for pathogen-specific, low-cost diagnostics for diseases. These biosensors require battery-free, user-friendly operation with minimal training.

5. Integrate with AI and data analytics

Biosensors could generate large, complex datasets that can be applied for precision health and diagnostics. Researchers could utilize machine learning for signal classification and predictive modeling and then create cloud-connected platforms for remote monitoring and providing population-level health insights.

6. Promote interdisciplinarity and innovation

Breakthroughs often occur at the intersection of fields in accelerating translation and commercialization. The recommendations to solve these problems encourage collaboration between engineers, materials scientists, data scientists, biologists, and clinicians.

The biological element itself is a living thing. When using a living thing as a sensing element to develop biosensors, the checklists for the successful commercialization are as follows:

1. Can the characteristics of the biosensing element be comparable to glucosidases?
2. Can all technical limitations, selectivity, sensitivity, and reproducibility be solved?
3. What are the service life and storage methods of the biological components?
4. How are biological components and transducers connected?
5. How should the biological reference materials be prepared?
6. How can mass production and quality be controlled?
7. How do we define usage time and storage time?
8. What is the cost and sale price after commercialization?
9. Does any competitor exist in the market?

If these problems can be solved, the academic research on biosensors will be able to achieve practical results. When comparing the characteristics of biosensors, especially the market competitors, the stripe tester biosensors have more market potential.

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