

## Recent advances in biosensing mechanism in glucose meter and how are they detecting the pressure pulse rate in it

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### Abstract

Various glucometer types have been developed over the last decades which used invasive, non or even real time methods. This paper examines the latest developments in biosensing systems relative to glucose meters, focusing on their capacity to quantify glucose concentrations and detect pulse rate. Among electrochemical biosensors subclassified into amperometric, potentiometric, and conductometric, they are still irreplaceable when it comes to glucose measurement, as they are highly sensitive and accurate. Advancements such as nanomaterial and motion sensing have made CGMs more effective and ergonomic by pointing out their underlying influence. Some alternatives which study the biological tissue non-invasively are Near-Infrared (NIR) and Raman spectroscopy but the problem is that it is expensive and face biological interference issues. Detection method such as Pressure pulse including Photoacoustic Spectroscopy (PAS) and Photoplethysmography (PPG) uses physiological signals for glucose and pulse rate control, making it painless and efficient. The possibility to integrate wearable devices with IoT technologies has led to the improvement of patient's autonomy in monitoring their health condition in real-time, as well as providing a complete overview of patients' metabolism and cardiovascular system. Moving away from traditional invasive methods and paying more attention to the patient's physiological signals, biosensors face certain issues such as motion artifacts, variability and limitations of the algorithm and despite these difficulties there are innovations in biosensors. This review also seeks to demonstrate how these innovations can revolutionize the management of diabetes and more so, health in general.

**Keywords:** Blood glucose level, biosensor, electrochemical sensor, noninvasive measurement, pressure pulse, Photoacoustic spectroscopy, photoplethysmography, near-infrared spectroscopy, wearable device, IoT in healthcare, diabetes mellitus.

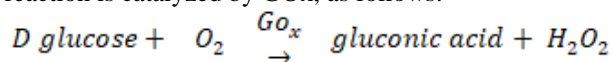
### Introduction

Blood Glucose monitoring system, most frequently referred as glucose meters or glucometers are essential instruments in the medical field for measurement of blood glucose levels and have significant importance in management of diabetes as well as various metabolic disorders. They all integrate sophisticated biosensing capabilities, primarily based on electrochemical activation schemes which provide sensitive, dependable and fast detection of glucose levels. Electrochemical biosensors have also assumed a central position in glucose meters given their ease of use, high sensitivity and accuracy in the measurement of small changes in glucose levels<sup>[1, 2]</sup>.

Electrochemical glucose biosensors are classified into three main categories based on their measurement principles: amperometric, potentiometric, conductometric and also the newly developed electrochemical sensors. Among the many varieties of sensors commonly used, the amperometric sensors can measure the electric current during the process of oxidized glucose readily with high sensitivity.

Whereas potentiometric sensors detect glucose concentrations based on changes in voltage resulting from the stirring of particular electrochemical reactions. Measurement of electrical conductivity related to the concentration of glucose is accomplished by conductometric sensors, which is an expanded variety of biosensing techniques. Taken together, all these methodologies contribute to the improvement of the repeatability and portability of glucose meters in different clinical and personal diabetes management situations<sup>[3, 4]</sup>.

The majority of glucose biosensors based on enzymatic reactions are utilized; however, GOx and GDH are the most commonly used biorecognition elements. Among these, GOx is especially preferred because it offers highest selectivity for glucose and also has remarkable stability in various conditions. These enzymes help in the oxidation of glucose a process that is typical of the glucose meters for their working. In the glucose oxidase mechanism,  $\beta$ -D-glucose is oxidised into gluconic acid and hydrogen peroxide ( $H_2O_2$ ) in the presence of molecular oxygen. The reaction is catalyzed by GOx, as follows:



The hydrogen peroxide generated in this reaction is subjected to further oxidation at a platinum electrode, resulting in the production of an electric current. This current is directly proportional to the glucose concentration in the blood sample, enabling the device to compute and present an accurate glucose level reading. The strong enzymatic activity and electrochemical principles guarantee that glucose meters deliver swift, reliable results crucial for efficient diabetes control<sup>[3]</sup>.

### Evolution of Glucose Monitoring Technology

Diabetes self monitoring of blood glucose level has come a long way from simple and ineffective techniques to more sophisticated and efficient techniques in the current world. These improvements have made a huge difference to the life of people who have Diabetes and provide better convenience, reliability and compatibility with easy health approaches.

In the past, the measurement of glucose was mostly done by the use of urine samples that indicated high levels of glucose. This approach involved a subjective estimation of samples of urine using a naked eye for the presence of glucose; it was usually unreliable and very inaccurate. Such limitations made it suboptimal for effective diabetes management. Blood testing methods are evident from the 1960s and included the use of colorimetric test strips that change color depending on the glucose concentration. Though more effective than the urine tests these methods were primarily used in clinical settings and cannot be used at home.

The development of portable BMG in 1970s is considered a revolution in managing the condition out of the hospital setting. These devices enabled people the flexible management of their glucose levels and gave them more autonomy regarding the health processes. However, early models of the calculator were large, complex, and sometimes would give out wrong results. Changes that occurred in the 1980s include enhanced strips which made it possible to have the Dextrometer with digital display, and this made the process easier to undertake. At this stage, test strips became more accessible to the public, making glucose testing accessible to far more people.

The next major development came with the advent of continuous glucose monitoring (CGM) systems in the end of the 1990s. The first CGM device had been approved by the FDA in 1999 and this had been able to record glucose data for up to 72 hours but the patients could not view the results in real-time. However, data was reviewed in a non-interventional manner by the healthcare providers. The subsequent years brought some enhancements including the Gluowatch and Medtronic's Guardian REAL-Time CGM, which has alarms for high and low glucose. However, these devices still relied on fingerstick tests for calibration, which reduced their convenience.

Everything changed after 2012 when real-time Continuous Glucose Monitors hit the market glasses. Appliances such as Abbott's FreeStyle Libre introduced in 2018, no longer required consumers to calibrate fingerstick and allowed consumers to scan the sensors for the glucose result. Full integration with smartphones added informed data and created tools that helped patients to better manage their diabetes.

The current glucose monitoring systems are more centralized, efficient and fully controlled systems compared to prior systems. The current CGMs can pair with an insulin pump to enable a process that releases insulin automatically depending on the glucose levels. This advancement has eliminated exhaustive patient monitoring and improved patient centered decision making. Moreover, constant studies have been made to discover new hassle-free glucose monitoring possessing no skin puncture. Novelties like Afon Technology's Gluowear suggest obtaining glucose data without using actual sensor needle.

Turning our attention to the future, there are exciting developments in the works that promise to have glucose monitoring go online. Improved data analysis together with the use of individual data will aid the monitoring and controlling of diabetes. These innovations are indicative of a shift towards patient centred care, where much of care delivery is underpinned through use of technology so that people can take responsibility for their own health care [5, 6, 7, 8, 9, 10]



Source: <https://flex.com/resources/blood-glucose-meters-50-years-of-transformation>

Fig 1: Blood-Glucose meter Evolution Since 1970-2020

### Recent Advancements in Glucose Meter Biosensors

Recent developments in glucose meter biosensors indicate enhancement of the features enhancing the CGM proficiency and convenience progressively, accurate, painless, and easy-to-use diabetic apparatuses. These glucose-monitoring innovations are changing the ways through which patients with diabetes can manage their disease or condition since they afford patients much more freedom and flexibility.

Electrochemical sensors continue to be the foundation for CGM technology advancement with new studies seeking to enhance the sensitivity, selectivity and stability of the sensors. The incorporation of new nanomaterials has improved these sensors through improving their accuracy in measuring glucose content and reducing their need for calibration and recalibration. Also, the latest sensor designs have incorporated other problems such as the motion artifacts, which used to affect the quality of data collected during movements. These enhancements guarantee electrochemical sensors to remain relevant and viable for use in CGM systems.

The introduced optical sensors are expected to provide non-invasive approaches to the conventional ones. Scholars like Hongli and Xudong have described a range of approaches, including Near Infrared (NIR) and Raman spectroscopy that are implemented by involving the interaction of light absorption within the body to check the glucose level without necessarily drawing blood. These methods give steady values by sampling glucose content in interstitial fluid. However, as with any technique, there are issues with the approach that requires attention before it is widespread, including high costs, interference of other biological molecules, and the complexity of processes that need to be performed in data analysis.

The new concept of CGM technology is based on flexibility in the structure of sensors thus, making them comfortable to wear. They can be easily wearable and have been developed to attach to the form of the body and be used to sense glucose in different body fluids such as perspiration, tears, and saliva. Such innovations as smart contact lenses for tear analysis and epidermal sensors for sweat detection can be named as the examples of such approach. Flexible sensors are promising, thanks to their decreased invasiveness and increased wearability, for more effective and less invasive glucose monitoring.

In addition, CGM wearable is slowly being incorporated into devices such as contact lenses, mouth guards, and wrist bands among others to make them appear more like ordinary items. This evolution towards discreet and multifunctional designs is intended to help to alleviate the prejudice around conventional glucose monitor devices. For example, modern continuous glucose monitoring systems are introduced with new connectivity methods so that users can easily connect it with a smartphone and other smart platforms to track the data in real time and receive deep analytics [11, 12, 13, 14]. Advancements in the optical and optical-absorption technologies showed which brought down glucose sensing much closer to be accurate real without having to invade the human body skin which is very important for the health of diabetics out there. They hold the potential to reduce the discomfort and methods endured with fingerstick methods and open up the way for more effective technologies and solutions. Of the studied methods under development, several have manifested enormous potential in providing accurate, invasive blood glucose estimations.

Near-Infrared (NIR) Spectroscopy is arguably one of the most researched methods for noninvasive glucose monitoring. This technique builds on the fact that NIR light can pass through biological tissues with relatively minimal scattering to measure glucose absorption bands at defined wavelengths. The noninvasive contactless nature of NIR spectroscopy and its ability to supply real-time glucose monitoring make NIR spectroscopy suitable for compact wearable applications. However, there are some drawbacks like the effect of interference from other biological molecules and the fact that high-level algorithms are required to resolve the glucose signals.

Mid Infrared (MIR) Spectroscopy works under the similar principle as NIR spectroscopy but it functions at longer wavelengths where glucose has vivid and selective absorption. This has the advantage of making MIR more sensitive at determining variations in concentrations of glucose and therefore making it highly useful. On the down side, the complex nature of the needed instrumentation and calibration points to a serious problem that hampers the device from being incorporated into consumer electronic products.

Raman Spectroscopy is another exciting method that provides analysis utilizing the inelastic scattering of a monochromatic light that comprises molecular vibrations selectively for glucose. This technique can give exact subject concentration of glucose than more interfered by water of biological tissues. Nevertheless, the Raman technique still has some drawbacks, including low signal intensity and sensitivity to background noise, thereby requiring the improvement of more efficient detection techniques [14, 15, 16, 17].

### Pressure Pulse Detection in Glucose Meters

The use of pressure pulse detection in glucometers is such a strategy with a clear and ambitious goal of improving the accuracy and invasiveness of blood glucose monitoring. This new method employs variations in blood volume and pressure, and seems to be a better solution than the standard fingertip blood sampling. With the help of the innovative methods such as Photoacoustic Spectroscopy (PAS) and Photoplethysmography (PPG), the pressure pulse detection systems are providing a wealthier set of very effective and comfortable glucose monitoring directions.

The Photoacoustic Spectroscopy (PAS) is a type of differential technique of analyzing glucose concentration through the interaction between tissues illuminated with pulsed laser light. Light will cause the glucose molecules in the tissue to heat up and produce pressure waves or acoustic signals. These signals can be used to measure glucose concentrations and they are detectable. Corresponding to glucose level, the amplitude of the pressure waves is also high and even low glucose concentration can be detected easily.

Some developments in PAS technology are PAS with 'two-wavelength pulsed' lasers that enhance precision since they are fashioned to focus on perceived glucose absorption. This approach means that in case of excitation at the first wavelength, fluorescence at the second wavelength is low and vice versa, thus reducing interferences from other biomolecules, leading to improved accuracy of glucose concentration detection. Previous experiments, including patrolling animal cells in petri dishes (*in vitro*) as well as in live subjects (*in vivo*), have shown much potential for PAS as a noncontact glucose sensing modality.

Photoplethysmography (PPG) is another new approach which relies on the periodic changes in blood volume. PPG on the other hand measures the waveform resulting from fluctuations in arterial blood volume in relation to beats. This waveform depends upon the physiological variables such as blood pressure, blood vessel flexibility, and glucose level. Through feature extraction from the PPG signal, it is possible for researchers to predict blood glucose levels.

However, complexity of this method is since PPG signal depends not only on vascular properties but also there are many factors like inter subject variability and motion artifact etc. To overcome such complications, the algorithms of machine learning have been used to learn from PPG data. These algorithms make the prediction of glucose levels precise by pinpointing the correlations and masking the interferences. Several trail studies have shown that PPG is feasible to use as a method of monitoring glucose levels without having to use invasive techniques for the management of diabetes.

Coherently, PAS and PPG signify promising advances toward minimally invasive glucose monitoring. While PAS quantifies with high sensitivity by accurate optical methods, PPG gains valuable information based on intrinsic physiologic rhythm of circulation. Both methods represent a perfect example of physiological knowledge in combination with the development of technology to create opportunities for constant and, therefore, comfortable monitoring of glucose levels. During further development of technologies and approaches, pressure pulse detection systems are evolving into highly effective and noninvasive tools for managing diabetes around the globe [18, 19, 20].

### Technologies for Pulse Rate Detection in Glucose Monitoring Devices

The modern glucose monitoring devices implemented technologies for the identification of pulse rate together with blood glucose level with increased accuracy and effectiveness. It also provides a better picture of a users' general health since it gives real time information of their metabolic and cardiovascular health. Overall integrating these novel sensing techniques with big data analytics has put these wearable devices into the forefront of portable health monitoring solutions.

Current glucose monitoring systems are founded on two optical techniques termed as Near-Infrared (NIR) spectroscopy and Photoplethysmography (PPG). NIR Spectroscopy employs red and near-infrared light to quantify glucose levels, because of its distinctive manner of absorbing light at precise wavelengths. It also facilitates the capacity to measure pulse rates by changes in light absorption resulting from the blood flow.

By integrating NIR technology, devices with optimum performance and convenience to the user and higher accuracy in the measurements can be achieved in days with optimum NMIR and SNIR for related gadgets. In the same way PPG sensors have established themselves as fundamentals of wearable health devices. Since PPG assesses the fluctuations of blood volume with each pulse beat, pulse rate is derived; in addition, PPG also enhances glucose measurement. Several of the most advanced glucose monitoring equipment today utilize PPG technology and provide valuable information on the users' metabolic and cardiovascular state on the spot.

Electrochemical sensors especially those using Reverse Iontophoresis have also improved enormously. This technique uses mild electric current to pump interstitial fluid or ISF which is then used to determine glucose levels in the body. Wearable devices like smart watches have upended continuous monitoring thanks to bendable electro-chemical sensors put into them, which allow noninvasive glucose and pulse rate tracking. By so doing, these wearables offer a non-invasive technique of monitoring that is convenient to the users in comparison to the prevailing invasive procedures.

Microwave sensing technologies are another young promising class of technologies. By using electromagnetic waves to transmit energy through body tissues, these devices evaluate glucose levels, changes in tissue dielectric properties. In addition, they can possibly monitor pulse rate if these properties related to blood circulation fluctuation are measured. This duality establishes microwave sensing as a potentially valuable resource for developing future non-invasive health monitoring systems, although its application remains in the developmental stage.

The use of IoT technology in glucose monitoring devices has made it even advanced than before. Through IoT integrated systems, data acquisition and use of data in a real-time manner benefits many users in particular giving them personal health information. For instance, while using wearable technology devices, glucose level and pulse rate can be checked frequently and the data fed to cloud where the data is analyzed using machine learning techniques with instructions being given in case the results of the measurements taken trend a certain direction. This connectivity improves personal health governance but also brings opportunities to telemedicine which allows health care practitioners to have continuous and unobtrusive access to the patient and engage when needed [21, 22, 23, 24, 25, 26].

Overall, enhancements of pulse rate detection along with glucose monitoring changed those devices in to health all in one device. Through a combination of optical, electrochemical, microwave and IoT technology, today's glucose monitors provide the highest levels of precision, versatility and usability for the end-users. These technologies are only going to get even better and with diabetes and overall health check they can change the way the healthcare is managed in the future.

## Challenges and Limitations of Pressure Pulse Rate Detection in Glucose Meters

Measuring glucose levels by applying PPR detection, including PPG, has its issue and limitations that disrupt accurate and reliable sensor readings. Such problems can be explained by biomedical and technical conditions.

### 1. Signal Quality and variability

Originally, the quality of PPG signals is very subjective, and the signals can be affected by many physiological factors, including blood volume changes, hemodynamics, and skin type and color. For example, changes in blood volume by as little as 5 percent can affect the quality of PPG signal and hinders the acquisition of true glucose measurements. Further, the amplitude is prone to other artifacts, which are peaks and inversions such as concentration of oxygen to hemoglobin [19].

### 2. Motion Artifacts

Interference originating from the patient's movements is quite problematic in PPR detection techniques. The problem with movement during measurement is that there will be addition of low frequency artefact onto one's pulse oximetry PPG waveform. To this end while works such as adaptive noise cancellation have been applied to reduce such effects, establishing a steady signal to noise ratio is still an endeavour. This kind of instability may limit the confidence of estimated glucose level obtained from PPG signals [16, 19].

### 3. Celebrational and Algorithmic Constraints

Therefore, the calibration of devices based on machine learning techniques presents certain conceptual limitations. Several works describe problems like data leakage and unreal assumptions made during preprocessing which distort results according to the authors. Furthermore, although algorithms can associate certain features of PPG with blood glucose measurement values, the efficacy of each algorithm in tracking intra-individual glucose fluctuations has not been documented sufficiently. This must leave questions about the effectiveness of these methods in clinical procedures [27].

### 4. Physiological Influences

There are several physiological factors influencing blood glucose and the waveform of PPG alike. Hemodynamics can also shift due to systemic diseases like metabolic syndrome, which can confuse causative links between the oscillations in PPG signals and actual glucose levels. Influencing factors such as age, BMI, mood, and breathing rate can add variability into the system which is not desirable and has to be compensated in the predictive model [19, 16].

### 5. Technological Constraints

The present technology for the continuous glucose monitoring, which is painless, has issues with precision resulting from the constraints in the designing of the task and effects from the surrounding. For instance, most current glucometers fail to meet the ISO accuracy specifications, several of them having MARD greater than the specified acceptable range. Moreover, the enzymatic detection methods that are widely used include certain errors that are associated with strip quality and handling techniques, such as poor blood samples collection [28].

## 6. Challenges to Clinical Implementation

In practical use, continuous glucose monitoring systems suffer from compliance problems where some patients may not adhere to the orders or develop discomfort from traditional methods such as finger pricking. These barriers have to be attained by noninvasive techniques, which must deliver accurate and timely readings in order to ward of precarious oscillations in glucose concentrations <sup>[16]</sup>.

### Discussion

Modern technological developments in biosensing systems in glucose meters have improved diabetes care by increasing accuracy, ease, and shift toward noninvasive techniques. Although high sensitivity and selectivity of traditional enzymatic glucose biosensors have been achieved, most of the techniques involved are invasive. Newer tissues have incorporated nanomaterials thus increasing the stability of these sensors and the times needed to calibrate them. Moreover, optothermal methods such as Near-Infrared (NIR), Mid-Infrared (MIR), and Raman spectroscopy are potential nondestructive techniques. These methods, however, exhibit a very high possibility in diverse applications; challenges including interference by biomolecules and high cost also act as limitations in their usage. Likewise, pressure pulse detection methods including PAS and PPG are also new ways of measuring glucose and pulse rate respectively. But, issues like motion artifacts, short coming of algorithms and physiological changes are known to affect the efficiency and accuracy of the device and hence should be addressed.

Integrating wearable technology offered by flexible sensors and IoT network advancement is a major shift towards personalized healthcare. Smart devices can now give instant feedback concerning glucose and cardiovascular health and improve user self-organization together with telemedicine. However, the currently available systems have limitations to signal stability, calibration accuracy and do not answer clinical needs. However, technological advancement continues to gain pace and improve so that the specific technologies are made even more available and efficient for given patient conditions.

### Conclusion

The progression of glucose monitoring technologies to exhibit increased accuracy further enhance their convenience as well as reduce discomfort commonly experienced by patients. Starting with enzymatic biosensors up to non-invasive optical and pressure pulse diagnostic techniques improvement of each method overcomes shortcomings of invasive measurements. Smartwatches and fitness trackers are examples of wearables based on IoT that can present an overview of people's health, biosensing in combination with real-time data processing. These have the potential to overcome current difficulties in the management of diabetes inclusive of interferences from signals and limitation in technologies. Subsequently, glucose monitoring system will not only enrich the diabetes care but also open new avenues for the portable and the non-invasive health monitoring which will mark new dawn in the healthcare delivery system.

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