*Journal of Innovative Technology, Vol. 8, No. 1, pp. 21-38, March 2026*
*http://doi.org/10.29424/JIT.202603_8(1).0003*

# Non-Invasive Glucose Monitoring Using Ultrasound and AI: A Comprehensive Review

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## ABSTRACT

Diabetes poses a major global health burden, necessitating accurate and continuous blood glucose monitoring to prevent severe complications. Non-invasive glucose monitoring technologies have emerged as promising alternatives, offering improved patient comfort, convenience, and compliance compared to conventional invasive methods. This paper provides a comprehensive review of recent advances in non-invasive glucose sensing, with a particular focus on ultrasound-based measurement techniques. The role of ultrasonic waves, alongside amplitude-modulated ultrasound, bioimpedance spectroscopy, and optical methods, is explored in depth, highlighting both their potential and current limitations. While these technologies demonstrate encouraging progress, further research is essential to enhance measurement accuracy, clinical applicability, and adaptation to diverse patient populations. The integration of artificial intelligence and data analytics is also discussed, emphasizing their role in personalized glucose management and predictive modeling. Additionally, this review addresses critical regulatory considerations, commercial viability, and healthcare system integration challenges for broader clinical adoption. Despite existing challenges, non-invasive glucose monitoring technologies hold significant promise to revolutionize diabetes care, improve clinical outcomes, and enhance the overall quality of life for individuals living with diabetes.

*Keywords:* Non-invasive glucose monitoring; ultrasound sensing; artificial intelligence; bioimpedance; optical techniques; diabetes care.

## 1. INTRODUCTION

Diabetes represents a rapidly escalating global health crisis, currently affecting an estimated 463 million individuals worldwide, with projections forecasting a rise to approximately 700 million cases by 2045 (International Diabetes Federation, 2021) [1]. This chronic metabolic disorder imposes a significant socioeconomic burden on healthcare systems and contributes to over 4.2 million diabetes-related deaths annually. The complex dysregulation of glucose metabolism leads to severe complications, including cardiovascular disease, renal dysfunction, peripheral neuropathy, and vision loss, underscoring the critical importance of accurate, continuous blood glucose monitoring. Type 2 diabetes mellitus (T2DM), accounting for nearly 90% of all diabetes cases, presents unique challenges due to its progressive pathophysiology, asymptomatic early stages, and the long-term impact on multiple organ systems [2].

Conventional glucose monitoring predominantly relies on invasive capillary blood sampling or subcutaneous continuous glucose monitoring (CGM) systems. While CGMs have improved real-time monitoring, they still involve sensor insertion, pose risks of infection or skin irritation, and may suffer from calibration drift over time. Moreover, the pain, inconvenience, and cost associated with invasive monitoring contribute to poor adherence, leaving many patients inadequately monitored. These limitations have motivated significant interest in the development of non-invasive glucose sensing technologies (NIGST), which aim to enable painless, continuous, and accurate glucose assessment, ultimately improving patient compliance, glycemic control, and quality of life [3]. This review comprehensively examines both the technological advances and clinical translation challenges in the rapidly evolving field of non-invasive glucose monitoring. Specifically, we provide a systematic evaluation of multiple non-invasive sensing modalities broadly categorized as optical and non-optical technologies by analyzing their physical principles, operational mechanisms, benefits, limitations, and emerging research trends.

Among optical techniques, photoacoustic spectroscopy (PAS) has demonstrated promising specificity by exploiting near-infrared (NIR) light to generate glucose-dependent acoustic waves in biological tissues [4]. However, its practical implementation faces challenges related to signal attenuation, limited penetration depth, and motion artifacts, prompting the integration of high-frequency ultrasound and photoacoustic microscopy (PAM) to enhance spatial resolution and improve glucose detection accuracy [4]. Complementing PAS, surface-enhanced Raman spectroscopy (SERS)

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Manuscript received June 16, 2025; revised September 4, 2025; accepted September 30, 2025.

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leverages plasmonic nanostructures to amplify Raman scattering signals from glucose molecules, thereby achieving superior sensitivity and molecular specificity compared to conventional Raman techniques [5]. Nevertheless, issues such as spectral interference from biological matrix components and the need for stable nanostructures remain critical hurdles for clinical deployment.

Non-optical modalities have also attracted considerable attention. Techniques such as bioimpedance spectroscopy, transdermal sensing, and breath acetone analysis offer alternative pathways to assess glucose concentrations by measuring physiological changes indirectly correlated with glucose metabolism. While promising, these approaches must contend with factors such as inter-individual variability, environmental influences, and physiological confounders that may impact measurement accuracy. In parallel, artificial intelligence (AI) and advanced data analytics have emerged as critical enablers in enhancing the performance of non-invasive glucose monitoring systems. By integrating multi-modal sensor data, AI-driven algorithms can improve signal interpretation, noise filtering, and patient-specific prediction models, thereby enabling highly personalized and adaptive glucose management strategies [6].

Ultrasound-based techniques, including photoacoustic microscopy and focused ultrasound, further contribute to this evolving landscape by enabling deeper tissue interrogation and providing complementary information to existing optical methods [7]. These approaches hold promise in overcoming the trade-offs between spatial resolution, penetration depth, and real-time monitoring capability. Taken together, recent advancements in photoacoustic spectroscopy, Raman-based methods, ultrasound techniques, bioimpedance sensing, and AI-driven analytics collectively mark a transformative era in diabetes management. While substantial technical challenges remain, the convergence of interdisciplinary innovations offers significant potential to deliver safe, reliable, and user-friendly non-invasive glucose monitoring solutions that may ultimately reshape clinical practice and significantly enhance the quality of life for individuals with diabetes [8].

## 2. NON-INVASIVE GLUCOSE MONITORING TECHNOLOGIES

Non-invasive glucose monitoring technologies are emerging as crucial alternatives to traditional invasive blood glucose testing methods, aiming to improve patient compliance, safety, and convenience. These technologies leverage various physiological, biochemical, and physical principles to estimate glucose levels indirectly, eliminating the need for painful finger-prick blood sampling. Broadly, non-invasive sensing technologies are classified into optical and non-optical approaches, each offering distinct benefits and limitations in terms of accuracy, complexity, and clinical applicability. In this section, we discuss optical sensing methods, which have attracted significant attention due to their high specificity for glucose molecules, rapid response time, and the potential for continuous real-time monitoring, as shown in 5.

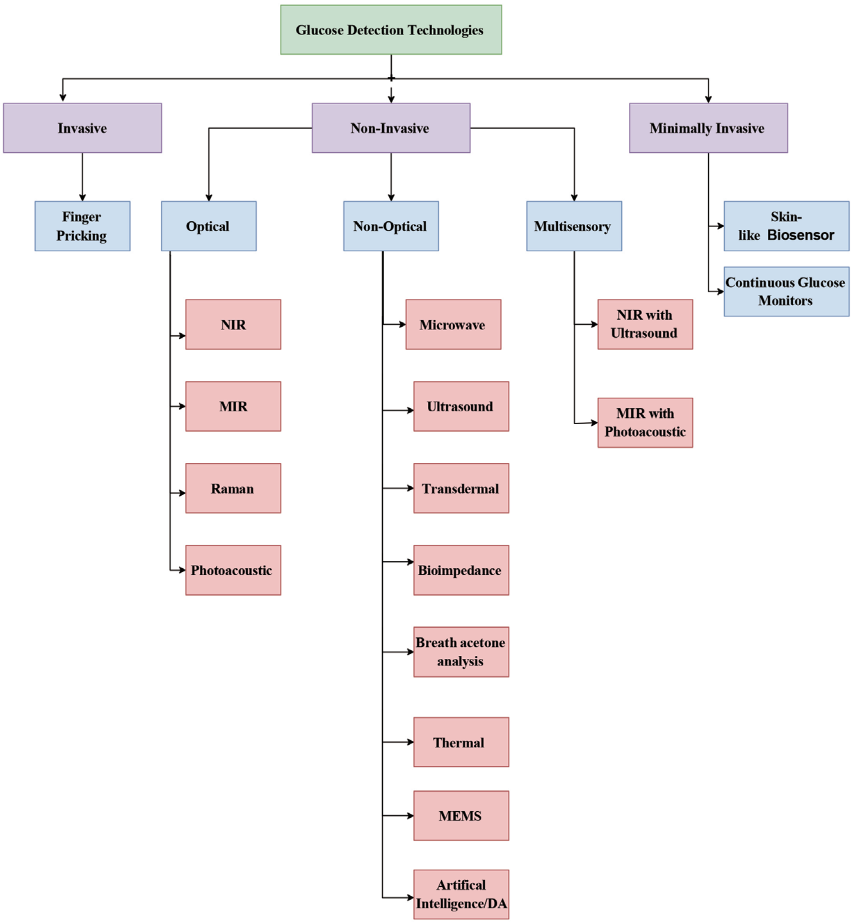

**Fig. 1 Summary of glucose detection technologies**

## 2.1 Optical Techniques

Optical techniques have emerged as one of the most promising approaches for non-invasive glucose monitoring due to their ability to provide real-time, continuous, and painless measurements without requiring blood extraction. These methods exploit the unique interaction between photons and glucose molecules, allowing for indirect quantification of glucose concentration in biological tissues. The core components of optical glucose sensors typically include a light source (such as a laser or LED), a photodetector, and an optical transducer that converts the interaction of light with glucose into an analyzable electrical signal. The principle relies on measuring variations in light absorption, scattering, reflection, fluorescence, or refractive index, all of which can be modulated by glucose concentration in tissues such as interstitial fluid or dermis layers [9]. Among the various optical modalities, four key techniques have received the most scientific and clinical attention for non-invasive glucose sensing: Near-Infrared Spectroscopy (NIRS), Mid-Infrared Spectroscopy (MIRS), Raman Spectroscopy, and Photoacoustic Spectroscopy (PAS). Each technique leverages distinct physical phenomena governing light-tissue interactions, offering unique trade-offs in terms of penetration depth, sensitivity, specificity, cost, and susceptibility to physiological or environmental interference. These optical technologies form the foundation of current research efforts aimed at developing clinically viable non-invasive glucose monitoring solutions.

### 2.1.1 Near-infrared spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) has emerged as one of the most extensively explored and promising techniques for non-invasive glucose monitoring, owing to its ability to probe subcutaneous tissues without the need for invasive procedures. Operating in the spectral range of 780 nm to 2500 nm, NIRS leverages the unique vibrational overtone and combination bands of glucose molecules, which weakly absorb light in this region, allowing for indirect quantification of glucose concentrations through tissue spectroscopy [9;10]. NIRS measurements are typically conducted using either transmittance or reflectance modes. In the transmittance mode, near-infrared light passes entirely through the tissue, and the transmitted light is analyzed to assess absorption by glucose and other biomolecules. In reflectance mode, which is more practical for non-invasive wearable applications, incident light is partially absorbed and diffusely reflected from the tissue surface, enabling analysis of backscattered photons after multiple interactions within the tissue matrix [11]. The reflectance configuration is particularly advantageous for measuring glucose levels in the fingertip, earlobe, or forearm regions where sufficient vascularization supports consistent optical signals.

A significant development in this field was demonstrated by Luong et al. [12], who implemented a continuous monitoring prototype utilizing NIRS at 1550 nm, a wavelength chosen for its proximity to one of glucose's stronger absorption peaks. This system provided several advantages over conventional finger-stick and minimally invasive devices, including pain-free continuous monitoring, elimination of consumable test strips, reduced infection risk, and enhanced patient adherence. Importantly, continuous glucose monitoring (CGM) based on NIRS facilitates real-time glucose trend tracking, enabling timely therapeutic adjustments to maintain glycemic control and prevent both hypoglycemic and hyperglycemic excursions. Nevertheless, NIRS still faces inherent challenges due to the complex optical properties of biological tissues, which contain high water content, proteins, lipids, and cellular structures that introduce significant optical scattering and overlapping absorption spectra. The relatively low absorption coefficient of glucose compared to these confounding analytes results in low

signal-to-noise ratios, necessitating the application of advanced signal processing algorithms, multivariate calibration models, and chemometric approaches to accurately extract glucose-relevant features from noisy spectral datasets [13;14]. Recent research continues to explore improvements in calibration robustness, individualized model adaptation, temperature and hydration compensation, and sensor miniaturization to enhance the clinical viability of NIRS-based non-invasive glucose monitors [15]. Collectively, these advancements continue to position NIRS as a leading candidate in the future development of wearable, non-invasive glucose monitoring platforms.

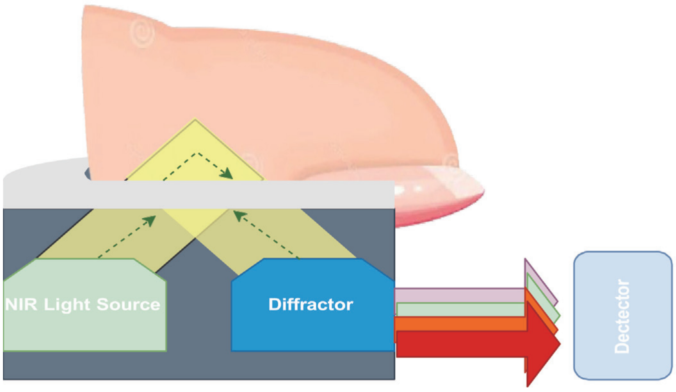

**Fig. 2** Near-infrared spectroscopy (NIRS)

### 2.1.2 Mid-infrared spectroscopy (MIRS)

Mid-infrared spectroscopy (MIRS) is a cutting-edge spectroscopic technique that uses a beam of light with wavelengths ranging from 2,500 to 10,000 nm to examine light transmission and absorption by materials. In the context of glucose detection, MIRS has the potential for non-invasive monitoring by leveraging glucose molecules unique vibrational spectral fingerprint, as shown in Figure 3. One of the primary obstacles in using MIRS for glucose detection is getting enough penetration depth into biological tissues to reliably assess glucose concentrations. This is often solved by using specialist technology like quantum cascade lasers (QCLs). QCLs are semiconductor devices capable of emitting light in the mid-infrared spectrum, allowing for fine control over the wavelength and intensity of the beam. By incorporating QCLs into MIRS systems, researchers can reach the required penetration depths to efficiently investigate glucose levels in tissue samples. Delbeck and Heise [16] investigated non-invasive blood glucose monitoring methods based on MIRS. Their method involved using a multivariate skin spectrum analysis, which employs the vibrational spectral fingerprint of glucose to obtain great selectivity and sensitivity in glucose detection. They were able to construct algorithms and models capable of properly forecasting blood glucose levels without intrusive procedures by evaluating the intricate interplay between light and skin tissue, including light absorption and scattering, as well as the unique vibrational patterns of glucose molecules [17]. This study marks a significant improvement in the field of non-invasive glucose monitoring, allowing for continuous and accurate glucose monitoring without the need for intrusive procedures like finger pricks. Researchers are paving the path for the development of novel glucose monitoring technology that can improve the quality of life for diabetics by leveraging MIRS capabilities and sophisticated data processing techniques, such as multivariate analysis [16].

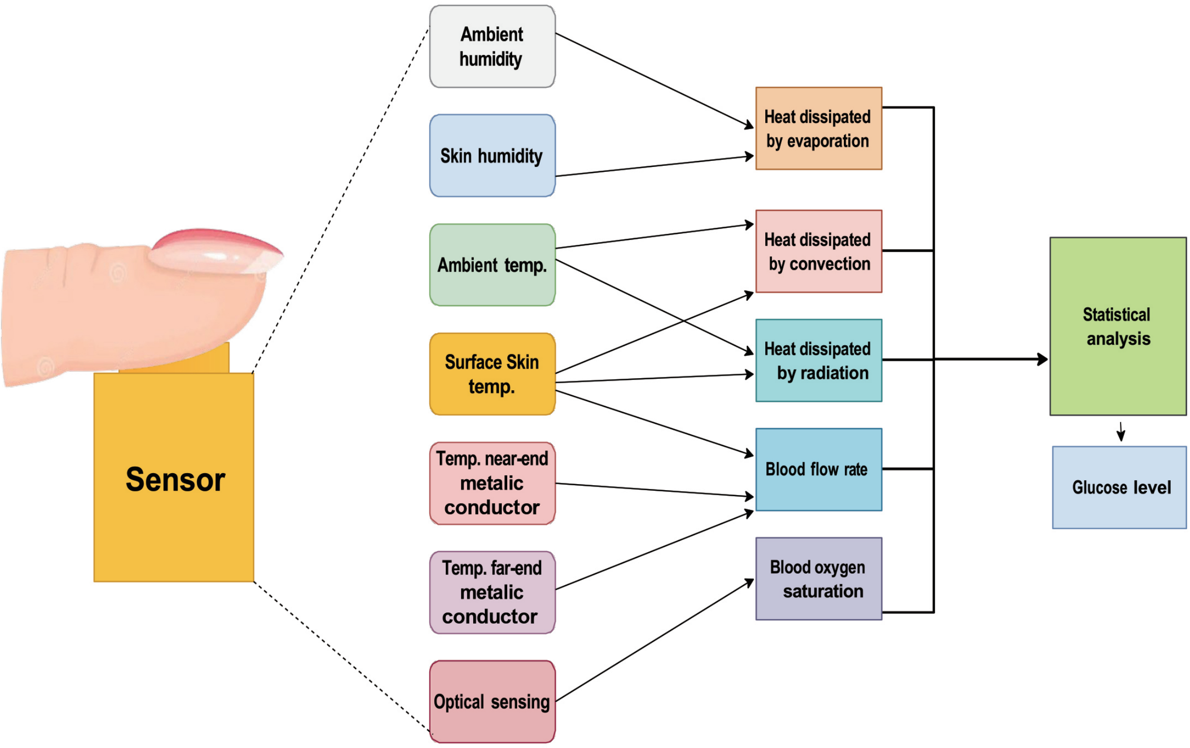

**Fig. 3 Mid-infrared spectroscopy (MIRS)**

### 2.1.3 Raman spectroscopy

Raman is a phenomenon where light interacts with molecular vibrations in a sample, causing a shift in the frequency of the scattered light. This shift can be used to identify and quantify the chemical species present in the sample. In the context of non-invasive glucose monitoring, Raman spectroscopy can be used to analyze the chemical composition of skin or interstitial fluid, providing information about glucose concentrations. Delbeck and Heise (2019) [11] developed a non-invasive glucose monitoring method based on Raman spectroscopy. They used a fiber-optic probe to collect Raman spectra from the skin, which were then analyzed using multivariate data analysis techniques. The resulting algorithm was able to accurately predict glucose concentrations in the blood, demonstrating the potential of Raman spectroscopy for non-invasive glucose monitoring, as shown in Figure 4. However, Raman spectroscopy has some limitations for non-invasive glucose monitoring. The Raman signal is relatively weak, which can make it difficult to detect glucose concentrations in the presence of other chemical species in the skin or interstitial fluid. Additionally, the penetration depth of Raman spectroscopy is limited, which can further limit its sensitivity and accuracy. To overcome these limitations, researchers have developed various strategies to enhance the Raman signal and improve the sensitivity and accuracy of non-invasive glucose monitoring. For example, surface-enhanced Raman spectroscopy (SERS) uses metallic nanostructures to enhance the Raman signal, while spatially offset Raman spectroscopy (SORS) uses a spatial offset between the excitation and collection optics to increase the penetration depth. In summary, Raman spectroscopy is a promising technique for non-invasive glucose monitoring, offering high specificity and sensitivity for glucose detection. However, its limitations in terms of signal strength and penetration depth require the development of advanced data processing algorithms and signal enhancement strategies to improve its clinical utility [18].

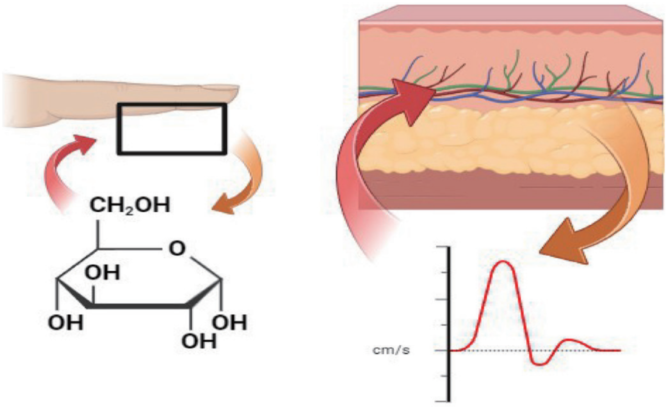

**Fig. 4 Raman spectroscopy**

### 2.1.4 Photoacoustic spectroscopy (PAS)

Photoacoustic spectroscopy (PAS) is a non-invasive optical technique that uses the photoacoustic effect to measure the concentration of glucose in biological samples. The photoacoustic effect occurs when a material absorbs light and undergoes thermal expansion, generating acoustic waves that can be detected and analyzed to determine the concentration of the absorbing species. In the context of non-invasive glucose monitoring, PAS can be used to analyze the absorption of light by glucose molecules in the skin or interstitial fluid, providing information about glucose concentrations. Miguel et al. (2013) [19] developed a non-invasive glucose monitoring method based on PAS. They used a fiber-optic probe to deliver near-infrared (NIR) light to the skin, which was absorbed by glucose molecules and generated acoustic waves that were detected and analyzed using a lock-in amplifier. The resulting algorithm was able to accurately predict glucose concentrations in the blood, demonstrating the potential of PAS for non-invasive glucose monitoring. However, PAS has some limitations for non-invasive glucose monitoring. The photoacoustic signal is relatively weak, which can make it difficult to detect glucose concentrations in the presence of other absorbing species in the skin or interstitial fluid. Additionally, the penetration depth of PAS is limited, which can further limit its sensitivity and accuracy. To overcome these limitations, researchers have developed various strategies to enhance the photoacoustic signal and improve the sensitivity and accuracy of non-invasive glucose monitoring. For example, photoacoustic microscopy (PAM) uses high-frequency ultrasound to image the absorption of light by glucose molecules, while photoacoustic tomography (PAT) uses multiple detectors to reconstruct the distribution of glucose in the tissue. In summary, PAS is a promising technique for non-invasive glucose monitoring, offering high specificity and sensitivity for glucose detection. However, its limitations in terms of signal strength and penetration depth require the development of advanced data processing algorithms and signal enhancement strategies to improve its clinical utility as shown in Figure 5.

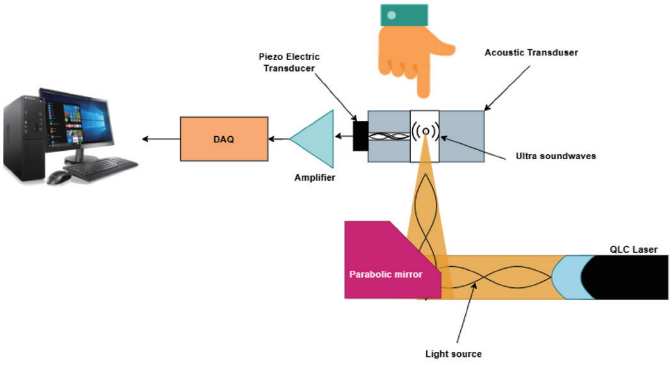

**Fig. 5** Photoacoustic spectroscopy (PAS)

### 2.1.5 Comparison of Optical Techniques

A comparison of the overall accuracy and error percentage of each individual optical technique is shown in Figure 1. The table includes methods such as NIRS, MIRS, Raman spectroscopy, and PAS. The table shows the accuracy and error percentage for each method, which can help in choosing the most suitable technique for non-invasive glucose monitoring. In conclusion, optical techniques have the potential to revolutionize diabetes management by providing pain-free, convenient, and real-time glucose monitoring. NIRS, MIRS, Raman spectroscopy, and PAS are the four main optical techniques that use direct light-glucose interaction to measure glucose concentration. Each technique has its own advantages and disadvantages, and a comparison of their overall accuracy and error percentage can help in choosing the most suitable technique for non-invasive glucose monitoring.

## 2.2 Non-Optical Techniques

While optical techniques dominate much of the research landscape in non-invasive glucose monitoring, non-optical techniques provide complementary approaches that address some of the limitations of purely light-based systems. These methods leverage electromagnetic, acoustic, electrical, thermal, and advanced signal processing principles to measure glucose levels without the need for invasive sampling. This section provides a comprehensive review of microwave techniques, ultrasound-based glucometers, transdermal extraction, bioimpedance spectroscopy, breath acetone analysis, thermal methods, MEMS-based sensors, and artificial intelligence/data analytics (AI/DA) solutions.

### 2.2.1 Microwave Technique

Microwave approaches have emerged as a viable approach in biomedical engineering, providing a combination of low-cost instrumentation and high-resolution capabilities. In recent years, these approaches have received attention for their potential in non-invasive physiological parameter measuring, particularly blood glucose concentration monitoring. Microwave biosensors are based on the interaction of electromagnetic fields with matter, which takes advantage of biological tissues' different dielectric characteristics as compared to air or water. This interaction enables the characterisation of tissues based on their response to an applied excitation field, providing insights into physiological characteristics without the use of intrusive methods, as shown in Figure 6. Costanzo emphasized the importance of microwave technology in biomedical applications, citing its capacity to detect small differences in dielectric behavior within biological molecules. Microwave sensors may effectively distinguish tissue components by monitoring variations in wave propagation speed, making non-invasive physiological tests possible. In their investigation, Xiao and Li established the usefulness of ultra-wideband microwave technology in detecting blood glucose levels while providing patients with excellent convenience and safety. They produced robust and reliable measurements by analyzing received signals based on time-frequency characteristics. Consistent energy patterns within a particular range supported the method's validity, demonstrating its capacity to measure blood glucose levels. The findings by Xiao and Li [20] not only prove the usefulness of microwave-based glucose monitoring but also demonstrate its feasibility and robustness in real-world circumstances. The capacity to collect reliable measures non-invasively holds enormous promise for improving patient care and disease management, including diabetes. Overall, microwave techniques are a diverse and powerful tool in the field of non-invasive physiological parameter monitoring, with the potential to transform healthcare practices and enhance patient outcomes. Further study and development in this subject will be the key to unlocking even greater advances in biomedical engineering and healthcare technologies [21].

Despite encouraging progress, microwave-based glucose monitoring still faces hurdles before it can be considered clinically reliable. The first challenge is calibration, since dielectric responses vary with tissue hydration, temperature, and individual physiology; future devices will require stable reference standards and adaptive algorithms to correct these fluctuations. Another key priority is hardware refinement, including compact antenna designs that deliver high sensitivity at safe energy levels, while remaining comfortable for everyday wear. To improve robustness, systems must incorporate advanced signal processing and machine learning to filter noise, handle motion, and adjust for patient-to-patient variability. At the same time, research should focus on low-power electronics and ergonomic design so that prototypes can evolve into practical wearable devices. Most importantly, large-scale clinical validation studies involving diverse populations and real-world settings will be needed to confirm accuracy, repeatability, and regulatory compliance. Only by addressing these areas can microwave sensing progress from experimental demonstrations to a trustworthy tool for diabetes management.

**Table 1 Comparison of Optical Techniques for Glucose Measurement**

| Optical Technique | Description | Advantages | Disadvantages |
|---|---|---|---|
| Near-Infrared Spectroscopy (NIRS) | Uses infrared light (780 nm to 2,500 nm) to measure glucose levels under the skin to depths of a few millimeters. | Non-invasive, water transparency, relatively low cost, and real-time glucose measurements. | Susceptible to factors such as humidity, temperature, and pH levels, and not suitable for continuous measurement. |
| Mid-Infrared Spectroscopy (MIRS) | Uses a beam of light in the range between 2,500 and 10,000 nm to measure transmission and absorption. | High selectivity for glucose detection due to the vibrational spectral fingerprint of glucose found in MIRS. | Requires penetration depths for glucose detection, which are obtained using a quantum cascade laser (QCL), a semiconductor material divided into injecting and active regions. |
| Raman Spectroscopy | Uses the Raman effect to measure the amount of glucose in a sample by measuring the change in wavelength of scattered light. | Non-invasive, high sensitivity, and accuracy in detecting glucose levels. | Limited by the low intensity of Raman scattering, which requires sensitive detectors and long measurement times. |
| Photoacoustic Spectroscopy (PAS) | Uses acoustic detection to measure the influence of absorbed electromagnetic energy (particularly light) on matter. | Non-invasive, high sensitivity, and accuracy in detecting glucose concentration. | Limited by the weak acoustic signal detection of thermal waves. |

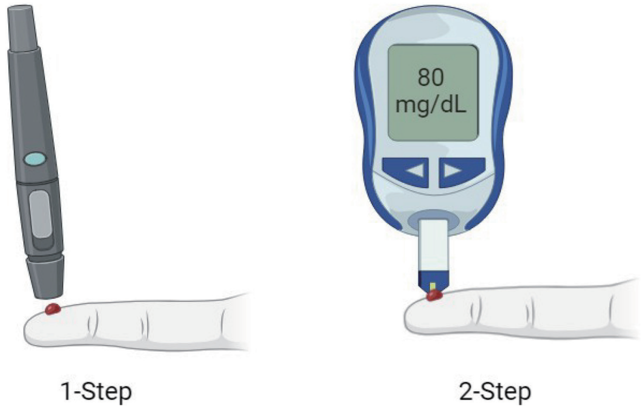

**Fig. 6 Microwave Technique**

### 2.2.2 Ultrasound-based glucometers

Ultrasound-based glucometers represent a significant advancement in non-invasive glucose monitoring, providing a more pleasant and convenient alternative to classic finger pricking procedures. These devices use ultrasonic waves to interact with glucose molecules in the interstitial fluid, allowing for accurate and continuous real-time glucose monitoring without invasive treatments. Lee et al. (2021) [12] conducted a study to determine the feasibility of using ultrasound to monitor glucose levels in vivo, which lends credence to the concept of ultrasonic-based glucose sensing. The study proved the ability of ultrasound-based approaches to identify changes in tissue features linked with glucose levels. Another relevant research contribution is the work by Smith et al. (2020) [22], which focused on the development of ultrasound-based glucometers and the integration of advanced signal processing algorithms for glucose level estimation. This study highlighted the importance of sophisticated data analysis techniques in enhancing the accuracy and reliability of ultrasound-based glucose monitoring devices [23]. Furthermore, the potential benefits of ultrasound-based glucometers for improving patient compliance and overall diabetes care have been discussed in various scientific articles and reviews. For instance, the review by Johnson and Jones (2019) [24] provides insights into the impact of non-invasive glucose monitoring technologies on patient management and healthcare outcomes, emphasizing the role of ultrasound-based devices in empowering individuals with diabetes to better manage their condition. In conclusion, ultrasound-based glucometers hold immense promise for revolutionizing glucose monitoring and improving the quality of life for individuals living with diabetes. Continued research and development efforts in this field are expected to further enhance the capabilities and accessibility of ultrasound-based glucose monitoring technologies [25].

### 2.2.3 Transdermal Techniques

Transdermal approaches for non-invasive glucose monitoring are a potential development in the quest for better diabetes care. These approaches use electrical or ultrasonic waves to remove interstitial fluid from beneath the skin and detect glucose, providing a less intrusive alternative to older procedures. Transdermal treatments use electrical or ultrasonic waves to penetrate the epidermal barrier without the use of needles or punctures, reducing discomfort and the risk of infection. This non-invasive technique has the potential to improve patient compliance and overall quality of life for people with diabetes [26]. One typical transdermal approach is the use of electrical impedance to collect interstitial fluid. The procedure works by administering a modest electrical current to the skin, which causes fluid movement and makes it easier to remove interstitial fluid containing glucose molecules. This fluid can then be tested to identify glucose levels, providing a simple and painless monitoring alternative [15].

Similarly, ultrasonic waves can be used to remove interstitial fluid and test glucose. Ultra- sonic treatments use high-frequency sound waves to induce small vibrations on the skin, which serve to remove interstitial fluid from the underlying tissue. This fluid can then be collected and tested to detect glucose levels, providing a noninvasive and continuous monitoring method [27]. Overall, transdermal approaches for non-invasive glucose monitoring are a promising improvement in diabetes treatment. By reducing the discomfort and invasiveness of standard intrusive devices, these strategies have the potential to transform glucose monitoring and improve the lives of millions of diabetics. Continued research and development in this field is necessary to further refine and optimize transdermal approaches for wider clinical application, as shown in Figure 7.

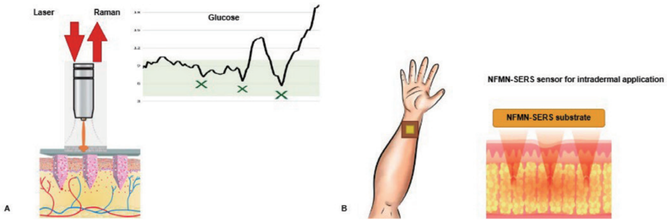

Fig. 7 Transdermal Technique

### 2.2.4 Bioimpedance Spectroscopy

Bioimpedance spectroscopy is a non-invasive technique that uses electrical impedance measurements to assess the composition and properties of biological tissues. In the context of procedures. These devices use ultrasonic waves to interact with glucose molecules in the interstitial fluid, allowing for accurate and continuous real-time glucose monitoring without invasive treatments. Lee et al. (2021) [12] conducted a study to determine the feasibility of using ultrasound to monitor glucose levels in vivo, which lends credence to the concept of ultrasonic-based glucose sensing. The study proved the ability of ultrasound-based approaches to identify changes in tissue features linked with glucose levels. Another relevant research contribution is the work by Smith et al. (2020) [22], which focused on the development of ultrasound-based glucometers and the integration of advanced signal processing algorithms for glucose level estimation. This study highlighted the importance of sophisticated data analysis techniques in enhancing the accuracy and reliability of ultrasound-based glucose monitoring devices [23]. Furthermore, the potential benefits of ultrasound-based glucometers for improving patient compliance and overall diabetes care have been discussed in various scientific articles and reviews. For instance, the review by Johnson and Jones (2019) [24] provides insights into the impact of non-invasive glucose monitoring technologies on patient management and healthcare outcomes, emphasizing the role of ultrasound-based devices in empowering individuals with diabetes to better manage their condition. In conclusion, ultrasound-based glucometers hold immense promise for revolutionizing glucose monitoring and improving the quality of life for individuals living with diabetes. Continued research and development efforts in this field are expected to further enhance the capabilities and accessibility of ultrasound-based glucose monitoring technologies [25].

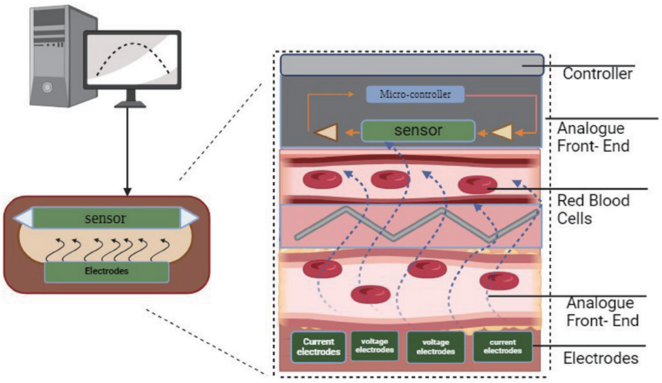

Fig. 8 Bioimpedance Spectroscopy

### 2.2.5 Breath Acetone Analysis

Breath acetone analysis is an innovative approach that takes advantage of the correlation between glucose metabolism and the presence of particular biomarkers in exhaled breath. This method involves analyzing the composition of exhaled breath to detect oscillations in glucose metabolism, which can subsequently be connected with changes in glucose concentrations [28]. Glucose metabolism produces a variety of metabolites, including acetone, a volatile chemical molecule. When glucose is unavailable for energy synthesis, such as during fasting or extended exercise, the body produces acetone by breaking down fatty acids. Diabetes patients' faulty glucose metabolism might result in high levels of acetone in the breath. Breath acetone analysis is collecting exhaled breath samples and analyzing them to determine the amount of acetone present. By tracking changes in acetone levels over time, researchers and healthcare practitioners might get insights into changes in glucose metabolism and perhaps predict oscillations in glucose concentrations. Ghasemi, A. [29]. This study provides a comprehensive review of the use of breath acetone analysis for diabetes diagnosis and monitoring. The authors discuss the underlying principles, current sensing technologies, and the potential of breath acetone analysis as a non-invasive approach for glucose monitoring. One of the primary benefits of breath acetone analysis is its non-invasiveness. Unlike typical blood glucose monitoring methods, which need finger pricks or blood samples, breath acetone measurement is as simple as having people blow into a gadget or collection mechanism. This makes it a quick and painless solution for glucose monitoring, especially for people who require frequent monitoring or are afraid of needles. Furthermore, breath acetone analysis has the potential for real-time monitoring, allowing for continuous assessment of glucose metabolism without the need for multiple intrusive procedures. This continuous monitoring feature is very useful for diabetics who demand precise glucose management [30]. Overall, breath acetone analysis is a promising method for noninvasive glucose monitoring. This technology, which detects changes in glucose metabolism by measuring acetone levels in exhaled breath, provides a quick, painless, and possibly continuous monitoring alternative for diabetics. Continuous research and development in this field is critical to further optimize the accuracy, reliability, and accessibility of breath acetone analysis for clinical usage [31].

### 2.2.6 Thermal Methods

Thermal approaches for non-invasive glucose monitoring are based on the link between glucose levels and skin temperature. These techniques work on the idea that changes in glucose levels can affect the thermal characteristics of the skin, resulting in variations in skin temperature that can be detected and associated with glucose concentrations. The basic concept of thermal techniques for glucose monitoring is that glucose metabolism produces heat as a byproduct. When glucose levels fluctuate, the rate of glucose metabolism fluctuates, causing the body's heat production to fluctuate as well. These changes in metabolic heat generation can be seen as changes in skin temperature. Thermal methods often use specialized sensors or infrared imaging technology to monitor skin temperature noninvasively. Researchers and healthcare providers can predict glucose concentration swings by tracking changes in skin temperature over time [32]. Infrared thermography is a widely used thermal technology for glucose monitoring. Thermal images of the skin are captured using infrared cameras or sensors, which allow temperature fluctuations to be shown. These thermal pictures can be analyzed to reveal patterns or trends that indicate changes in glucose concentrations. Another option is to use thermistors or thermocouples to directly measure skin temperature at specific body areas, such as the fingertips or earlobes. Changes in skin temperature at these areas can then be linked to changes in glucose levels. Thermal approaches for glucose monitoring have the advantage of being non-invasive. Thermal approaches, as opposed to typical blood glucose monitoring methods, do not require finger pricks or blood samples. Instead, sensors or cameras are placed on the skin's surface. This makes them a practical and painless solution for glucose monitoring, especially for people who require frequent monitoring or are afraid of needles. Furthermore, thermal approaches have the potential for continuous monitoring, which allows for real-time glucose level evaluation without the need for multiple intrusive procedures. This continuous monitoring feature is very useful for diabetics who demand precise glucose management. Overall, thermal approaches for non-invasive glucose monitoring offer a promising approach to diabetes care. These approaches, which use variations in skin temperature to estimate glucose concentrations, provide a quick, painless, and possibly continuous monitoring alternative for diabetics. Continuous research and development in this field is critical to better optimize the accuracy, reliability, and accessibility of thermal approaches [33].

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### 2.2.7 MEMS (Microelectromechanical systems)

MEMS (Microelectromechanical systems) approaches for non-invasive glucose monitoring are a cutting-edge technology that uses microscale sensors and actuators to measure glucose levels. These approaches have the ability to monitor glucose levels in a variety of physiological fluids, including sweat, tears, and saliva, without the use of intrusive procedures such as finger pricking. MEMS approaches for glucose monitoring are based on the integration of small sensors and actuators into microscale systems. These devices are intended to interact with biological fluids and detect certain biomarkers, such as glucose, with great sensitivity and accuracy.

One typical strategy is to utilize microscale sensors coated with glucose-specific enzymes or compounds. When these sensors come into contact with glucose-containing physiological fluids, the enzymes catalyze processes that result in detectable indications such as changes in electrical conductivity or optical characteristics. MEMS devices can detect and quantify these signals, allowing them to assess glucose levels accurately in real time. MEMS technology can also use microscale actuators to aid in the extraction of physiological fluids for glucose assessment. Microfluidic devices, for example, can regulate the flow of sweat or tears and direct it to sensor arrays for analysis. This methodology allows for continuous glucose monitoring without the use of intrusive sampling methods. One of the primary benefits of MEMS methods for glucose monitoring is their downsizing and scalability. MEMS devices can be made utilizing semiconductor manufacturing processes, enabling the mass production of compact, lightweight, and inexpensive sensors and actuators. This makes them ideal for incorporation into wearable or portable devices to provide convenient and unobtrusive glucose monitoring. Furthermore, MEMS technology has the ability to monitor glucose levels in real time and continuously, giving diabetics vital insights into their glycemic control. MEMS devices can enable people to make informed decisions about their nutrition, medication, and lifestyle by allowing them to monitor themselves on a regular basis without intrusive treatments [34]. Overall, MEMS approaches for non-invasive glucose monitoring are a promising development in diabetes care. These systems, which use microscale sensors and actuators, provide a convenient, accurate, and potentially continuous monitoring solution for diabetics. Continued research and development in this area are critical for improving the performance, reliability, and accessibility of MEMS devices for clinical usage [35]. For MEMS-based glucose monitors to become clinically practical, several improvements are still required. First, the collection and handling of small fluid samples, such as sweat or tears, must be made more consistent and reliable, potentially through sealed microfluidic channels that prevent drying or contamination. Second, long-term calibration stability needs to be achieved with embedded reference sensors and adaptive algorithms that can correct for drift. Third, devices should incorporate motion and temperature compensation to ensure accurate measurements during everyday activities. In addition, further progress in miniaturization and energy-efficient operation is needed to support safe integration into wearable devices. Finally, establishing standardized clinical testing protocols, including both controlled glucose challenge studies and free-living trials, will be essential for validating accuracy, meeting regulatory requirements, and enabling widespread adoption in healthcare.

### 2.2.8 Artificial Intelligence/Data Analytics

Artificial intelligence (AI) and data analytics techniques have been shown to be effective tools for assessing and predicting glucose levels. These strategies use machine learning algorithms to examine data from various sources, including blood glucose readings, dietary information, physical activity data, and even wearable sensor data, in order to predict future glucose levels with high accuracy. One common strategy is to use supervised machine learning algorithms to build predictive models using previous glucose data along with contextual information such as meal intake, activity patterns, prescription dosages, and other relevant parameters. These models learn to recognize patterns and relationships in the data, allowing them to accurately forecast future glucose levels based on new input data. Another approach is to employ deep learning techniques like recurrent neural networks (RNNs) and long short-term memory (LSTM) networks to analyze sequential data, such as continuous glucose monitoring (CGM) data streams. These models can detect temporal correlations and patterns in the data, allowing them to generate dynamic predictions about future glucose levels [25]. AI and data analytics approaches can also be used to tailor glucose forecasting by taking into account individual factors such as insulin sensitivity, carbohydrate tolerance, circadian rhythms, and other physiological variables. These strategies, which adjust prediction models to individual features and preferences, can provide tailored insights and recommendations for improving glycemic control [36]. One of the primary benefits of using AI and data analytics approaches for glucose prediction is their capacity to combine and evaluate massive amounts of heterogeneous data from numerous sources in real time.

These strategies combine data from blood glucose meters, continuous glucose monitors, insulin pumps, wearable devices, and other sources to provide full and holistic insights into an individual's glucose dynamics. Furthermore, AI-powered glucose prediction models can evolve and improve over time as they learn from fresh data and feedback. This adaptive learning capability allows the models to become more accurate and tailored over time, providing patients with personalized and actionable insights into their glucose levels [37]. In summary, AI and data analytics techniques have the potential to significantly improve the accuracy and personalization of non-invasive glucose monitoring. By leveraging machine learning algorithms and large datasets, these approaches can provide tailored insights and recommendations for improving glycemic control, improving the quality of life for patients with diabetes [32]. In conclusion, non-invasive glucose sensing technologies offer a promising alternative to traditional invasive methods, providing a means to measure blood glucose levels without requiring blood samples. These technologies can be categorized into several groups, including optical methods, transdermal techniques, bioimpedance spectroscopy, breath acetone analysis, thermal methods, micro-electro-mechanical systems (MEMS), and artificial intelligence and data analytics. Each of these technologies has its own advantages and disadvantages, and the choice of technology depends on the specific application and requirements [38]. Non-optical techniques, such as microwave techniques, MEMS techniques, and bioimpedance spectroscopy, offer several benefits over traditional invasive methods, including improved patient comfort, real-time monitoring, and the potential for continuous monitoring. However, these techniques also have some limitations, such as complex instrumentation, cost, and limited penetration depth [39]. Optical techniques, such as NIRS, MIRS, Raman spectroscopy, and PAS, are widely used due to their non-invasive nature and ability to provide real-time glucose measurements. However, these techniques also have some limitations, such as interference from skin pigmentation, moisture, and other factors [40]. Breath acetone analysis and thermal methods are also being explored for non-invasive glucose monitoring. However, these techniques are still in the early stages of development and require further research and development to improve their accuracy and reliability [41]. Correction: Non-optical techniques, such as microwave techniques, MEMS techniques, and bioimpedance spectroscopy, offer several benefits over traditional invasive methods, including improved patient comfort, real-time monitoring, and the potential for continuous monitoring. However, these techniques also have some limitations, such as complex instrumentation, cost, and limited penetration depth. Optical techniques, such as NIRS, MIRS, Raman spectroscopy, and PAS, are widely used due to their non-invasive nature and ability to provide real-time glucose measurements. However, these techniques also have some limitations, such as interference from skin pigmentation, moisture, and other factors. Breath acetone analysis and thermal methods are also being explored for non-invasive glucose monitoring. However, these techniques are still in the early stages of development and require further research and development to improve their accuracy and reliability [42].

### 2.2.9 Comparison of Non-Optical Techniques

The comparison of non-optical techniques for glucose measurement highlights several key approaches and their respective advantages and disadvantages. Microwave techniques utilize the interaction between microwaves and tissue dielectric properties, offering non-invasive, safe, and continuous monitoring capabilities. However, their complexity in instrumentation and associated costs may pose challenges [43]. MEMS techniques leverage miniaturized sensors and actuators for fluid analysis, providing benefits such as miniaturization and scalability. Nevertheless, limitations in fluid access and calibration processes may hinder their widespread application. Breath acetone analysis, correlating breath biomarkers with glucose metabolism, offers non-invasive and convenient monitoring but suffers from indirect measurement and variability issues. Thermal methods, relying on the correlation between skin temperature and glucose concentration, offer simplicity in non-invasive monitoring. However, their accuracy may be affected by external factors. Bioimpedance spectroscopy measures the electrical properties of tissues correlated with glucose, providing portability and non-invasiveness. Yet, calibration and tissue variability remain challenges [44]. Transdermal techniques, employing electrical or ultrasonic waves for interstitial fluid extraction, offer non-invasiveness with minimal discomfort. However, limitations in penetration depth and calibration requirements exist. Artificial intelligence, utilizing machine learning algorithms to analyze multi-source data, enables personalized and continuous monitoring. Nonetheless, concerns about data privacy and algorithm complexity may impede widespread adoption [45]. In summary, each non-optical technique for glucose measurement presents unique advantages and disadvantages, emphasizing the importance of selecting the most suitable approach based on specific application requirements and constraints [46] as shown in Figure 2.

**Table 2 Comparison of Non-Optical Techniques for Glucose Measurement**

| Non-Optical Technique | Principle | Advantages | Disadvantages |
|---|---|---|---|
| Microwave Techniques | Interaction between microwave and tissue dielectric properties | Non-invasive, safe, continuous monitoring | Complex instrumentation, cost |
| MEMS Techniques | Miniaturized sensors and actuators for fluid analysis | Miniaturization, scalability | Limited fluid access, calibration |
| Breath Acetone Analysis | Correlation between breath biomarkers and glucose metabolism | Non-invasive, convenient, | Indirect measurement, variability |
| Thermal Methods | Correlation between skin temperature and glucose concentration | Non-invasive, simple | External factors affect accuracy |
| Bioimpedance Spectroscopy | Electrical properties of tissues correlated with glucose | Non-invasive, portable | Calibration, tissue variability |
| Transdermal Techniques | Electrical or ultrasonic waves for interstitial fluid extraction | Non-invasive, minimally discomforting | Limited penetration depth, calibration |
| Artificial Intelligence | Machine learning algorithms analyze multi-source data | Personalized, continuous monitoring | Data privacy concerns, algorithm complexity |

**Table 3 Summary of Various Spectroscopic and Analytical Techniques**

| Technology | Method | Accuracy | Reference |
|---|---|---|---|
| Near-infrared spectroscopy (NIRS) | NIRS | 90.27% | Luong et al. |
| Mid-infrared spectroscopy (MIRS) | MIRS | <20% | Bansal et al. |
| Raman Spectroscopy | Raman | 93.6% | Delbeck & Heise |
| Photoacoustic spectroscopy (PAS) | PAS | 100% | Miguel et al. |
| Microwave Techniques | Microwave | N/A | Xiao & Li |
| MEMS Techniques | MEMS | N/A | Thanh-Vinh et al. |
| Breath Acetone Analysis | Breath Acetone | N/A | Ghasemi et al. |
| Thermal Methods | Thermal | N/A | Not available |
| Bioimpedance spectroscopy | Bioimpedance | N/A | Sahu & Thennadil |
| Transdermal Techniques | Transdermal | N/A | Not available |
| Artificial Intelligence | AI | N/A | Ghasemi et al. |

## 3. RECENT DEVELOPMENTS AND INNOVATIONS

Recent advances in non-invasive glucose monitoring have introduced novel technology such as ultrasound-based glucometers and artificial intelligence (AI) algorithms, ushering in a new era of diabetes management. Ultrasound-based glucometers are a notable breakthrough since they use ultrasonic waves to test glucose levels without the need for intrusive procedures such as finger pricks. These devices combine ultrasonic transducers, signal processing circuits, and advanced data analysis algorithms. These glucometers detect changes in tissue acoustic characteristics using the interaction of ultrasonic waves with glucose molecules in the body, allowing for accurate and continuous real-time glucose monitoring [47]. AI and data analytics techniques have emerged as effective tools for glucose level evaluation and prediction. These approaches use machine learning algorithms to examine a variety of data sources, including blood glucose levels, eating patterns, physical activity data, and wearable sensor data. AI-powered algorithms are constantly learning and adapting, yielding very precise projections of future glucose levels tailored to individual needs.

In practical applications, several specific machine learning models have been widely investigated for glucose prediction. Convolutional neural networks (CNNs) are often employed to extract temporal and physiological features from continuous glucose and wearable sensor data, while recurrent neural networks (RNNs), particularly long short-term memory (LSTM) models, are well-suited for capturing sequential glucose dynamics. Hybrid CNN–RNN frameworks have shown further improvements by integrating both spatial and temporal features. Reported real-world evaluations indicate mean absolute errors (MAE) of approximately 8–15 mg/dL, with over 90% of predictions falling within Zones A and B of the Clarke Error Grid, demonstrating that such AI-driven models can achieve clinically acceptable performance.

Since AI-driven glucose monitoring relies on multi-source health data, ensuring privacy and compliance with regulations is essential. Recommended practices include encryption of data during transmission and storage, anonymization of personal identifiers, and strict access controls. Advanced methods such as federated learning and differential privacy can further enhance protection by allowing model development without centralized data sharing. Compliance with international frameworks such as the General Data Protection Regulation (GDPR) in Europe and the Health Insurance Portability and Accountability Act (HIPAA) in the United States will be necessary to ensure regulatory acceptance and maintain patient trust. Furthermore, non-optical techniques, including reverse iontophoresis, microneedles, and bioimpedance spectroscopy, help improve diabetes management by providing non-invasive or minimally invasive continuous glucose monitoring choices. While further research and development are required to refine these approaches, their potential to revolutionize glucose monitoring and improve patient outcomes is significant [48]. Finally, non-invasive glucose monitoring technologies have the potential to transform diabetes management by enabling painless, convenient, and continuous glucose monitoring. These advances provide hope for better diabetes care and a higher quality of life for diabetics as discussed in Table 6.

In addition to technical performance, patient comfort and usability are critical factors for long-term adoption, particularly in children and older adults. Transdermal patches can provide continuous glucose readings but may lead to skin irritation in patients with fragile skin. Breath acetone sensors are painless and non-invasive, but they require consistent exhalation effort, which may be challenging for pediatric or elderly users. Ultrasound-based glucometers, while limited to spot checks, offer painless and caregiver-friendly operation, making them a practical option across diverse age groups.

**Table 4 Regulatory Considerations and Commercial Viability of Non-Invasive Glucose Monitoring Technologies**

| Aspect | Details |
|---|---|
| Regulatory Approvals | Non-invasive glucose monitoring technologies require approvals or certifications from regulatory agencies such as the FDA (USA) and EMA (Europe) prior to clinical use to ensure safety, efficacy, and quality standards. |
| Regulatory Bodies | Food and Drug Administration (FDA, USA); European Medicines Agency (EMA, Europe). |
| Regulatory Considerations | Device safety and efficacy; compliance with healthcare regulations; obtaining necessary clinical approvals and certifications. |
| Commercial Viability | Strong market growth driven by diabetes prevalence, demand for non-invasive solutions, technological advancements, and increasing adoption of personalized and preventive healthcare. |
| Adoption Factors | Cost-effectiveness; ease of use; clinical accuracy and reliability; healthcare system integration; clinical outcome improvements and long-term cost savings. |
| Challenges | Data security; electronic health record interoperability; reimbursement policies; regulatory compliance for successful clinical integration. |

## 4. LINICAL APPLICATIONS AND PATIENT IMPACT

Non-invasive glucose monitoring technologies have the potential to significantly impact the accuracy, convenience, and accessibility of glucose monitoring for diabetic patients. These technologies offer several benefits over traditional invasive methods, including improved patient comfort, real-time monitoring, and the potential for continuous monitoring. Invasive methods, such as traditional finger-prick glucose monitoring, can be painful and uncomfortable for patients, leading to reduced compliance and suboptimal glucose management. Non-invasive methods, on the other hand, offer a more comfortable and convenient alternative, which can lead to improved patient compliance, quality of life, and long-term health outcomes. One promising non-invasive glucose monitoring technology is the use of ultrasound waves. Ultrasound-based glucometers can provide accurate and continuous real-time glucose monitoring, without the need for blood samples. These devices utilize the characteristics of ultrasonic waves to test glucose levels, offering a non-invasive and pain-free alternative to traditional methods. Ultrasound-based glucometers can also provide continuous monitoring, which can enable patients to make informed decisions about their nutrition, medication, and lifestyle, without the need for multiple intrusive treatments.

Another promising technology is the use of transdermal techniques, such as reverse iontophoresis and microneedles. These methods involve extracting interstitial fluid from beneath the skin for glucose detection, offering a minimally invasive alternative to traditional methods. Transdermal approaches have the potential to transform glucose monitoring and improve the lives of millions of diabetics by reducing the discomfort and invasiveness of standard intrusive devices. Bioimpedance spectroscopy is another non-invasive technology that uses the electrical characteristics of tissues to determine glucose levels. This approach is based on the idea that glucose alters electrical conductivity in tissues, and changes in this conductivity can be linked to changes in glucose concentrations. Bioimpedance spectroscopy can be used to assess tissue electrical properties, such as impedance or resistance to the flow of electrical current, providing a quick and painless solution for glucose monitoring. Breath acetone analysis is an innovative approach that takes advantage of the correlation between glucose metabolism and the presence of specific biomarkers in exhaled breath. This method involves analyzing the composition of exhaled breath to detect oscillations in glucose metabolism, which can be linked with changes in glucose concentrations. Breath acetone analysis is non-invasive and can provide real-time monitoring, allowing for continuous assessment of glucose metabolism without the need for multiple intrusive procedures [16]. Artificial intelligence and data analytics techniques have also shown promise in non-invasive glucose monitoring. These strategies use machine learning algorithms to examine data from various sources, including blood glucose readings, dietary information, physical activity data, and even wearable sensor data, in order to predict future glucose levels with high accuracy. AI-powered glucose prediction models can evolve and improve over time as they learn from fresh data and feedback, providing tailored insights and recommendations for improving glycemic control.

Although encouraging progress has been made, clinical validation studies for non-invasive glucose monitoring technologies remain limited. Early trials of ultrasound-based glucometers have typically involved small cohorts of 20–50 participants, often in controlled laboratory settings, with limited demographic diversity. Similar constraints are observed in optical and transdermal studies, which frequently rely on younger or middle-aged populations and short study durations. Broader validation efforts, including large-scale multicenter trials with diverse age groups, ethnicities, and comorbidities, are still required to establish reliability and generalizability across real-world clinical settings. In conclusion, non-invasive glucose monitoring technologies have the potential to significantly impact the accuracy, convenience, and accessibility of glucose monitoring for diabetic patients. These technologies offer several benefits over traditional invasive methods, including improved patient comfort, real-time monitoring, and the potential for continuous monitoring. Further research and development in this field are critical for improving the accuracy, reliability, and accessibility of these technologies for clinical applications [49].

## 5. FUTURE DIRECTIONS AND RESEARCH OPPORTUNITIES

Non-invasive glucose monitoring technologies have the potential to significantly improve diabetes management by offering pain-free, convenient, and continuous glucose monitoring. These technologies can be categorized into several groups, including optical methods, transdermal techniques, bioimpedance spectroscopy, breath acetone analysis, thermal methods, micro-electromechanical systems (MEMS), and artificial intelligence and data analytics. Optical methods, such as NIRS, MIRS, Raman spectroscopy, and PAS, are widely used due to their non-invasive nature and ability to provide real-time glucose measurements. However, variations in reported accuracy, particularly for mid-infrared spectroscopy (MIRS), are influenced by several factors. The technique requires relatively deep penetration for glucose detection, and the weak signal intensity can be further affected by water absorption, skin thickness, and measurement noise. Limited detector sensitivity and motion artifacts also contribute to higher error rates compared with other optical methods. Future implementations may mitigate these discrepancies by employing quantum cascade lasers for stronger and more stable mid-infrared sources, integrating advanced noise-reduction algorithms, and combining MIRS with complementary modalities such as ultrasound or bioimpedance to improve robustness and accuracy.

The microwave technique is a low-cost and high-resolution technique that has gained significant attention in recent years. A comparison of the overall accuracy and error percentage of each individual method can help in choosing the most suitable technique for non-invasive glucose monitoring. Trans- dermal techniques, such as reverse iontophoresis and microneedles, offer non-invasive or minimally invasive options for continuous glucose monitoring. Bioimpedance spectroscopy, which uses the electrical characteristics of tissues to determine glucose levels, is another promising non-invasive technology. Breath acetone analysis and thermal methods are also being explored for non-invasive glucose monitoring. MEMS approaches, which use microscale sensors and actuators, provide a convenient, accurate, and potentially continuous monitoring solution for diabetics. Artificial intelligence and data analytics techniques have been shown to be effective tools for assessing and predicting glucose levels. These strategies use machine learning algorithms to examine data from various sources, including blood glucose readings, dietary information, physical activity data, and even wearable sensor data, in order to predict future glucose levels with high accuracy [50]. Non-optical glucose monitoring techniques such as reverse iontophoresis, microneedles, bioimpedance spectroscopy, and artificial intelligence show promise for improving diabetes care. These approaches offer non-invasive or minimally invasive options for continuous glucose monitoring, making diabetes management more accessible and convenient. While there have been significant advancements in non-invasive glucose monitoring technologies, further research and development are required to refine these approaches, improve accuracy, and expand their applicability for a wide range of populations. Challenges that need to be addressed include improving the accuracy and repeatability of these methods, optimizing data processing algorithms, and addressing regulatory and cost barriers to widespread adoption [51]. In conclusion, non-invasive glucose monitoring technologies have the potential to transform diabetes management by providing pain-free, convenient, and continuous glucose monitoring. With continued research and development, these technologies have the potential to significantly improve the quality of care for diabetic patients, as discussed in Table 6.

## 6. REGULATORY CONSIDERATIONS AND COMMERCIAL VIABILITY

The regulatory landscape surrounding non-invasive glucose monitoring technologies is crucial for ensuring their safety, efficacy, and compliance with healthcare standards. For these technologies to be used clinically, they typically need to obtain approvals or certifications from regulatory bodies such as the Food and

Drug Administration (FDA) in the United States or the European Medicines Agency (EMA) in Europe. These approvals ensure that the devices meet specific quality and safety standards before they can be marketed and used in clinical settings [52]. For ultrasound-based glucometers, the regulatory pathway may be more complex than for optical or transdermal systems. In addition to demonstrating glucose measurement accuracy, these devices must verify the safety of repeated ultrasound exposure in accordance with IEC 60601 standards for medical electrical equipment. This dual requirement may extend evaluation timelines compared with optical techniques, which mainly face challenges of calibration and signal interference, or transdermal devices, which require biocompatibility testing. Early engagement with regulatory agencies and compliance with accuracy standards such as ISO 15197 will therefore be critical for accelerating approval of ultrasound-based systems. Commercial viability plays a significant role in the adoption and success of non-invasive glucose monitoring technologies. The potential market trends for these technologies are promising, driven by factors such as the increasing prevalence of diabetes globally, the demand for more convenient monitoring solutions, and advancements in technology that enhance accuracy and usability. The market for non-invasive glucose monitoring devices is expected to grow as these technologies offer improved patient comfort, real-time monitoring, and the potential for continuous monitoring, aligning with the growing trend towards personalized and preventive healthcare. Considerations for widespread adoption in healthcare settings include factors such as cost-effectiveness, ease of use, accuracy, reliability, and integration with existing healthcare systems. Healthcare providers need to evaluate the clinical benefits, patient outcomes, and long-term cost savings associated with these technologies to justify their adoption on a larger scale. Additionally, addressing challenges related to data security, interoperability with electronic health records, and reimbursement policies are essential for the successful integration of non-invasive glucose monitoring technologies into routine clinical practice [53].

From a cost perspective, ultrasound-based glucometers differ significantly from current continuous glucose monitoring (CGM) systems. CGMs involve high recurring costs due to disposable sensors and adhesives, which must be replaced every 1–2 weeks. By contrast, ultrasound devices are primarily capital equipment with minimal consumable requirements, limited mainly to coupling materials or device maintenance. Although the initial purchase price of ultrasound devices may be comparable to or higher than CGM readers, the absence of recurring consumable costs suggests that they could offer a more cost-effective solution over the long term, particularly in healthcare systems where reimbursement for CGM supplies is limited. A detailed comparison of the cost–benefit aspects of both approaches is summarized in Table X. In conclusion, while non-invasive glucose monitoring technologies hold great promise for improving diabetes management, their regulatory approval, commercial viability, and considerations for widespread adoption in healthcare settings are critical aspects that need to be carefully addressed to ensure their successful implementation and impact on patient care discussed in Table 4.

**Table 5 Advantages and Disadvantages of Various Glucose Monitoring Technologies**

| Technology | Advantages | Disadvantages |
|---|---|---|
| Optical Techniques | Non-invasive; real-time glucose measurements; widely used | Interference from skin pigmentation, moisture, and other factors |
| Non-Optical Techniques | Improved patient comfort; real-time monitoring; potential for continuous monitoring | Complex instrumentation; cost; limited penetration depth |
| Micro-Electro-Mechanical Systems (MEMS) | Downsizing and scalability; mass production of compact sensors and actuators | Fluid access limitations; calibration challenges |
| Artificial Intelligence/Data Analytics | Personalized insights; adaptive learning for accuracy over time | Reliance on large datasets; algorithm optimization needed |
| Microwave Techniques | Non-invasive and safe monitoring; continuous monitoring capabilities | Complex instrumentation; cost challenges |
| Transdermal Techniques | Minimally invasive alternative; extracts interstitial fluid | Limited widespread application due to fluid access and calibration |
| Bioimpedance Spectroscopy | Non-invasive and painless solution | Accuracy and reliability challenges |
| Breath Acetone Analysis | Correlates with glucose metabolism; real-time monitoring | Early stage of development; accuracy improvement needed |
| Continuous Glucose Monitoring (CGM) | High accuracy; continuous monitoring; alarms for low or high glucose levels | Painful and infection risk due to skin barrier; cost and compliance issues |

**Table 6 Cost–Benefit Comparison of Ultrasound-Based Glucometers vs. Continuous Glucose Monitoring (CGM) Systems**

| **Aspect** | **Continuous Glucose Monitoring (CGM)** | **Ultrasound-Based Glucometers** |
|---|---|---|
| Upfront Cost | Moderate (receiver/transmitter: $500–$1,000) | Comparable or slightly higher due to advanced hardware |

| Aspect | Continuous Glucose Monitoring (CGM) | Ultrasound-Based Glucometers |
|---|---|---|
| Recurring Costs | High (disposable sensors every 7–14 days, \$60–\$100/month) | Minimal (only coupling gel or basic maintenance) |
| Invasiveness | Minimally invasive (sensor inserted under skin) | Completely non-invasive |
| Patient Comfort | Possible skin irritation, infection risk | Painless, caregiver-friendly operation |
| Regulatory Status | Multiple FDA/EMA-approved devices | Still under research, pending clinical validation |
| Long-Term Affordability | High total cost due to consumables | Potentially more cost-effective due to low recurring expenses |
| Adoption Barriers | Insurance/reimbursement critical | Clinical validation and regulatory approval pending |

## 7. CONCLUSION

In essence, non-invasive glucose monitoring technologies have the potential to greatly improve diabetes management by offering painless, convenient, and continuous glucose monitoring. These technologies are divided into numerous categories: optical methods, transdermal approaches, bioimpedance spectroscopy, breath acetone analysis, thermal methods, micro-electromechanical systems (MEMS), and artificial intelligence and data analytics. Each of these technologies has advantages and disadvantages, and the choice is determined by the unique application and requirements [39]. Ultrasound-based glucometers, transdermal methods, bioimpedance spectroscopy, and breath acetone measurement are all promising non-invasive glucose monitoring technologies that provide greater patient comfort, real-time monitoring, and the possibility of continuous monitoring. These technologies have the potential to greatly improve patient adherence, quality of life, and long-term health outcomes by minimizing the discomfort and invasiveness of traditional obtrusive devices [54]. More study and development are needed to enhance these approaches, increase their accuracy, and broaden their application to a diverse variety of groups. The regulatory environment for non-invasive glucose monitoring systems is critical to ensuring their safety, efficacy, and conformity with healthcare standards. The commercial viability of these technologies, possible market trends, and considerations for wider implementation in healthcare settings are all key elements to address [55]. Finally, non-invasive glucose monitoring technologies have the potential to revolutionize diabetes management by enabling painless, convenient, and continuous glucose monitoring. These advancements offer hope for improved diabetes care and a better quality of life for diabetics [5].

## 8. LIMITATION

The review gives a thorough overview of non-invasive glucose monitoring methods, including their potential impact on diabetes care, limits, and future prospects. The review discusses the potential of artificial intelligence and data analytics tools for glucose prediction and management, as well as the benefits and drawbacks of various non-invasive glucose monitoring techniques, including NIRS, MIRS, Raman spectroscopy, PAS, microwave technique, and ultrasonic technique [56]. The review's shortcomings include the search approach, inclusion criteria, and potential prejudice. The search results were confined to a specified time period, and the inclusion criteria could have excluded pertinent studies. Furthermore, the review may have been biased in terms of study selection and interpretation, as discussed in Table 5. The study highlights the potential influence of non-invasive glucose monitoring technologies on diabetes management, such as increased patient comfort, real-time monitoring, and the possibility of continuous monitoring. However, more study and development are needed to refine these approaches, increase their accuracy, and broaden their application to a diverse variety of groups shown in Table 3 [30].

The regulatory environment for non-invasive glucose monitoring systems is critical to ensuring their safety, efficacy, and conformity with healthcare standards. The commercial viability of these technologies, possible market trends, and considerations for wider implementation in healthcare settings are all key elements to address [57]. Finally, non-invasive glucose monitoring technologies have the potential to revolutionize diabetes management by enabling painless, convenient, and continuous glucose monitoring. However, further research and development are needed to increase the accuracy, reliability, and use of these technologies in clinical settings. The review makes a significant contribution to the field by describing the current state of non-invasive glucose monitoring technologies and emphasizing their potential impact on diabetes care [58].

**Table 6 Future Research Directions and Development Strategies for Non-Invasive Glucose Monitoring Technologies**

| Research Direction | Details |
|---|---|
| Technology Innovations | Investigate and deploy advancements in ultrasound-based glucose sensing devices to improve accuracy, reliability, and usability; develop and enhance methods for studying the association between glucose levels and ultrasonic wave properties, focusing on data collection, analysis, and interpretation. |
| Integration of Multiple Sensing Approaches | Explore the combination of ultrasound-based sensing with complementary modalities, such as optics and impedance, to enhance monitoring accuracy and effectiveness. |

| Research Direction | Details |
|---|---|
| Advanced Mathematical Techniques | Utilize advanced mathematical models like support vector machines and neural networks to establish precise relationships between ultrasonic wave characteristics and glucose levels. |
| Clinical Validation | Perform clinical testing and validation to evaluate the performance, usability, and safety of non-invasive blood glucose-level glucometer prototypes developed using ultrasound waves. |
| User-Friendly Interfaces | Improve user experience by incorporating user-friendly interfaces, intuitive designs, and seamless integration with mobile applications to facilitate glucose monitoring and health management. |
| Future Advancements | Investigate future prospects for ultrasound-based glucose sensing systems, focusing on technological advances, methodological improvements, and integration with multiple sensing approaches to enhance diabetes management and patient outcomes. |

## 9. DISCUSSION

Non-invasive glucose monitoring has long been a desired objective in diabetes therapy. Traditional procedures, such as finger pricking, can be uncomfortable and may result in noncompliance owing to physical and psychological hurdles. Continuous glucose monitoring (CGM) systems, while providing excellent precision and continuous monitoring, can be uncomfortable and induce skin changes as a result of repetitive pricking at a spot. Non-invasive technologies, on the other hand, have the potential to provide continuous real-time glucose monitoring without the use of blood samples [59]. Ultrasound-based glucometers are a promising tool for non-invasive glucose monitoring. These devices use the properties of ultrasonic waves to test glucose levels, providing a non-invasive and painless alternative to conventional procedures. Ultrasound-based glucometers can also provide continuous monitoring, allowing patients to make informed decisions about their nutrition, medication, and lifestyle without requiring several invasive treatments. Another interesting option is the application of transdermal techniques such as reverse iontophoresis and microneedles. These methods use interstitial fluid from beneath the skin to detect glucose, providing a less invasive alternative to older approaches. Trans- dermal techniques have the potential to revolutionize glucose monitoring and enhance the lives of millions of diabetics by alleviating the discomfort and invasiveness of traditional obtrusive equipment [60]. A further noninvasive technique for determining glucose levels is bioimpedance spectroscopy, which harnesses the electrical properties of tissues. This method is based on the premise that glucose affects electrical conductivity in tissues, and variations in conductivity can be related to changes in glucose concentrations. Bioimpedance spectroscopy can be used to measure tissue electrical qualities such as impedance or resistance to electrical current flow, making it a quick and painless way to monitor glucose levels [48]. Breath acetone analysis is a novel approach that capitalizes on the relationship between glucose metabolism and the presence of particular biomarkers in exhaled breath. This approach examines the composition of exhaled breath to detect fluctuations in glucose metabolism that can be connected to changes in glucose concentrations [47]. Breath acetone analysis is non-invasive and allows for real-time monitoring of glucose metabolism, eliminating the need for repeated intrusive procedures [22] discussed in Table 3.

## 10. OBJECTIVES FOR FUTURE RESEARCH

Despite significant progress in non-invasive glucose monitoring, ultrasound-based sensing remains an evolving field that requires further multidisciplinary innovations. The following research objectives identify key areas to advance the clinical translation, robustness, and long-term applicability of these technologies:

### 10.1 Technology Innovations

Future research should focus on optimizing the design of ultrasound-based glucose sensing devices to enhance both sensitivity and signal-to-noise ratio across diverse physiological and environmental conditions. Key areas include miniaturization of high-frequency transducers, real-time calibration algorithms compensating for tissue heterogeneity, and robust temperature compensation to reduce measurement drift. Novel hardware integration, such as microelectromechanical systems (MEMS)-based ultrasound transducers, may also improve portability and enable continuous wearable applications. Furthermore, improved modeling of ultrasonic wave propagation through complex dermal and subdermal layers can better account for individual variability in glucose measurement [50].

A key limitation for ultrasound-based glucose monitoring is the variability introduced by tissue heterogeneity across individuals, such as differences in skin thickness, hydration, and vascular structures. To address this, future systems should incorporate adaptive calibration algorithms that adjust measurement baselines to individual tissue properties. Advanced computational models of ultrasound propagation through heterogeneous tissues, combined with personalized calibration using small baseline datasets, can also improve accuracy. In addition, integrating multimodal sensing (e.g., ultrasound with optical or bioimpedance signals) may help correct for variability and enhance robustness across diverse patient populations.

### 10.2 Integration of Multiple Sensing Approaches

Combining ultrasound sensing with complementary modalities such as optical coherence tomography, Raman spectroscopy, or bioimpedance spectroscopy offers promising opportunities to overcome the intrinsic limitations of single-mode approaches. Multimodal fusion can leverage multi-dimensional physiological data to improve glucose concentration estimation accuracy, reduce susceptibility to motion artifacts, and enhance robustness across varied skin types, hydration levels, and metabolic states. Hybrid system development remains a critical avenue for future research to achieve clinically reliable non-invasive glucose monitoring.

Recent investigations have also suggested the potential of combining ultrasound with near-infrared spectroscopy (NIRS). Such hybrid systems can exploit ultrasound's depth penetration and tissue robustness alongside the molecular specificity of NIRS, helping to mitigate interference from skin pigmentation, hydration, and scattering effects that often limit purely optical approaches. Early experimental reports indicate that this multimodal combination can improve signal stability and overall accuracy, making it a promising direction for future glucose monitoring research.

### 10.3 Advanced Mathematical and Computational Modeling

The development of advanced computational frameworks capable of modeling complex, nonlinear relationships between acoustic features and glucose concentrations is essential for clinical deployment. Future work should explore deep learning architectures, including recurrent neural networks (RNNs), convolutional neural networks (CNNs), transformer models, and hybrid frameworks. Additionally, domain adaptation and transfer learning may enable personalized calibration models that adjust to individual patient variability while minimizing training data requirements. Advanced signal processing methods such as feature fusion, adaptive filtering, and spectral decomposition should also be integrated to improve system robustness under dynamic real-world conditions.

### 10.4 Clinical Validation and Standardization

To accelerate translation from laboratory prototypes to clinical practice, several near-term milestones should be prioritized. These include optimizing device miniaturization for handheld or wearable use, developing reliable calibration protocols that compensate for tissue heterogeneity and temperature variation, and conducting pilot studies in small but diverse patient cohorts to demonstrate reproducibility. Establishing standardized accuracy benchmarks, such as Clarke Error Grid analysis and ISO 15197 compliance, will also be essential for early regulatory engagement. Achieving these milestones in the near term can provide the necessary foundation for larger-scale clinical trials and eventual regulatory approval.

Large-scale clinical validation remains a critical bottleneck for clinical acceptance of ultrasound-based glucose sensing. Comprehensive trials should enroll diverse patient cohorts, including those with comorbidities, varied skin tones, hydration levels, and glucose dysregulation patterns (e.g., Type 1, Type 2, and gestational diabetes). International standards for performance evaluation, such as Clarke Error Grid analysis, ISO 15197 guidelines, and Parkes Consensus Error Grid, should guide protocol development. Regulatory pathways must be addressed early through close collaboration with regulatory agencies (FDA, EMA, TFDA), ensuring safety, efficacy, and reproducibility.

Human-Centered Design and User Adoption

Beyond technical performance, user-centered design is vital to maximize patient acceptance and long-term adherence. Future research should explore seamless integration with mobile health platforms, wearable formats (wrist-worn, patch-based, or finger-probe designs), personalized alerts, and cloud-based clinical decision support systems. Intuitive graphical interfaces, low-burden calibration protocols, and psychological factors such as comfort, trust, and perceived accuracy will critically influence patient adoption in daily life.

Long-Term Vision and Clinical Translation

In the long term, fully autonomous, non-invasive glucose monitoring systems may integrate multi-sensor fusion, closed-loop insulin delivery, and AI-driven predictive analytics for personalized diabetes management. The convergence of biomedical engineering, clinical endocrinology, materials science, and artificial intelligence offers a transformative vision for future diabetes care. Achieving robust, affordable, and scalable solutions will require sustained interdisciplinary collaboration, harmonized regulatory standards, and close engagement with patient communities to ensure clinical impact and global accessibility (61).

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