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Non-Invasive Glucose Sensing: A Comprehensive Review of FTIR, Bio-Impedance, and Multimodal Approaches

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Abstract*—Non-invasive glucose monitoring (NIGM) is a critical advancement for diabetes management, offering a painless alternative to frequent blood sampling. Single-modality techniques—optical spectroscopy (FTIR, Raman, NIR) and electrical methods (bio-impedance)—face limitations such as low specificity, interference from water and tissue components, and variability due to physiological factors. Fourier-Transform Infrared (FTIR) spectroscopy, particularly in Attenuated Total Reflectance (ATR) mode, provides high molecular specificity, while bio-impedance offers sensitivity to glucose-induced tissue conductivity changes. Recent studies suggest that combining these complementary modalities into multimodal NIGM systems can overcome individual shortcomings, enhancing accuracy, robustness, and real-time monitoring capability. This review synthesizes the state-of-the-art in FTIR and bio-impedance-based glucose sensing, compares single- and multimodal approaches, and identifies challenges such as signal interference, calibration variability, and continuous monitoring implementation. Literature demonstrates that multimodal systems coupled with advanced data fusion and chemometric modeling improve correlation with invasive measurements, indicating strong potential for clinically viable, patient-friendly NIGM solutions.

Keywords*—Non ‚invasive glucose monitoring (NIGM), Raman spectroscopy, FTIR, data fusion, multimodal sensing, diabetes.

I. INTRODUCTION

Diabetes mellitus is a long-term metabolic disorder marked by high blood sugar levels. If not managed well, it can lead to serious issues like heart disease, nerve damage, eye problems, and kidney failure [1,6]. Managing diabetes effectively requires regular checking of blood glucose levels to keep them within a healthy range and avoid long-term problems. Traditional methods for glucose monitoring, such as finger-prick tests and continuous glucose monitoring (CGM) systems, give accurate readings. However, they are invasive, painful, and not convenient for frequent use, which can lead to poor patient adherence [1,6].

These challenges have sparked significant research into non-invasive glucose monitoring (NIGM) technologies. These aim to measure blood glucose without breaking the skin. NIGM has the potential for painless, real-time, continuous monitoring, which can greatly enhance patient comfort and adherence [2,10,13]. In the last twenty years, several optical and electrical methods have been explored. These include near-infrared (NIR) spectroscopy, Raman spectroscopy, Fourier-Transform Infrared (FTIR) spectroscopy, and bio-impedance spectroscopy (BIS) [2,3,4,10].

FTIR spectroscopy, especially in Attenuated Total Reflectance (ATR) mode, has gained interest for its ability to detect glucose-specific molecular vibrations directly and without damaging the sample [4,7]. In contrast, bio-impedance spectroscopy estimates glucose levels indirectly by measuring changes in the electrical properties of tissues. This allows for real-time monitoring and integration with wearable sensors [10,15]. While each technique has its strengths, they also come with limitations. FTIR can be affected by water and the environment, while bio-impedance lacks glucose specificity and may be influenced by physiological variations.

To tackle these issues, researchers have begun using multimodal approaches. These combine different techniques like FTIR, Raman spectroscopy, and bio-impedance. By using the strengths of each method and covering for their weaknesses, multimodal NIGM systems show potential for better accuracy, reliability, and continuous monitoring [8,9].

This review analyzes current NIGM techniques, focusing on FTIR spectroscopy and bio-impedance. It highlights multimodal approaches, compares their effectiveness, identifies research gaps, and suggests future paths for clinically useful non-invasive glucose monitoring solutions.

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II. LITERATURE REVIEW

A. Historical Background and Overview of NIGM Techniques

Non-invasive glucose monitoring (NIGM) has been researched for several decades as an alternative to traditional blood glucose measurement methods. Early studies aimed to reduce patient discomfort while keeping clinical accuracy, which led to exploring optical, electrical, and hybrid sensing techniques [1], [2]. Over time, advancements in spectroscopy, signal processing, and sensor technology have allowed the development of various NIGM approaches, each with its own advantages and limitations [9], [10], [13]. This section offers an overview of the main NIGM techniques, focusing on optical, electrical, and emerging methods.

1) Optical Techniques

Optical techniques are the most studied group of NIGM methods because they do not require contact and can allow for continuous monitoring [2], [9]. These methods take advantage of how electromagnetic radiation interacts with glucose molecules or the physiological changes caused by glucose.

Near-Infrared (NIR) spectroscopy was one of the first optical methods examined for non-invasive glucose sensing. It works in the wavelength range of about 700 to 2500 nm and depends on overtone and combination vibrational bands of glucose-related molecular bonds [2], [10]. Its main benefits include deeper tissue penetration, low water absorption, and compatibility with compact devices. However, NIR glucose sensing struggles with weak glucose-specific signals, strong spectral overlap with other tissue components, and high sensitivity to physiological variability, which limits its accuracy and reliability in clinical settings [2], [9], [13].

Raman spectroscopy offers molecular fingerprinting by using inelastic scattering of light, giving it high chemical specificity for glucose detection [3], [11]. Raman-based NIGM can identify glucose-specific vibrational modes directly, making it appealing for accurate glucose measurement. Nevertheless, Raman spectroscopy encounters issues like low signal intensity, interference from tissue fluorescence, and sensitivity to ambient noise [3], [14]. A lot of research focuses on optimizing excitation wavelengths and system setups to reduce fluorescence effects and improve the signal-to-noise ratio [5], [11], [12].

Fourier Transform Infrared (FTIR) spectroscopy, especially in the mid-infrared range, has been studied for its ability to explore fundamental vibrational modes of glucose, providing better chemical specificity than NIR methods [2], [10]. The use of Attenuated Total Reflection FTIR (ATR-FTIR) allows for measurements with less water interference and shallow penetration depths suitable for biological samples [4], [7]. FTIR-based glucose sensing benefits from strong glucose absorption features and works well with chemometric analysis, but limited tissue penetration and sensitivity to hydration and temperature changes remain major challenges [9], [13].

2) Electrical Techniques

Electrical techniques for NIGM mainly measure changes in the electrical properties of biological tissues caused by variations in glucose concentration. One notable method is Bio-impedance Spectroscopy (BIS), which has gained interest for its simplicity and non-optical nature.

BIS measures the frequency-dependent electrical impedance of tissues, reflecting changes in ionic conductivity, cell membrane capacitance, and extracellular fluid composition [9], [10]. Since glucose concentration affects osmotic balance and tissue dielectric properties, impedance measurements at different frequencies can be linked to glucose levels. BIS systems have been studied for wearable and continuous monitoring applications due to their low cost and easy integration [15], [17].

Despite these advantages, electrical techniques have low glucose specificity and heavily depend on factors like temperature, hydration, sweat, and electrode placement [9], [13]. These issues have limited the standalone use of BIS for accurate glucose monitoring, leading to research into combined and data-fusion approaches [8], [17].

3) Other Techniques

Alongside optical and electrical methods, several other NIGM techniques have been explored. Optical Coherence Tomography (OCT) has been looked into for glucose sensing by detecting changes in tissue scattering and refractive index caused by glucose, but its indirect measurement method limits specificity [9], [10].

Fluorescence spectroscopy uses glucose-sensitive fluorescent markers or natural fluorophores, which offer high sensitivity but often require invasive labeling or implantation, affecting their non-invasive nature [9], [13].

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Transdermal extraction methods, like reverse iontophoresis, try to pull interstitial glucose through the skin using electrical currents, but issues related to skin irritation, calibration drift, and time lag have hindered widespread use [9], [15].

New approaches like microwave and terahertz spectroscopy use changes in dielectric properties linked to glucose concentration and can penetrate deeper into tissues. While promising, these methods currently face challenges such as system complexity, safety concerns, and sensitivity to environmental factors [10], [17].

B. Focused Review of FTIR Spectroscopy for Glucose Sensing

Fourier Transform Infrared (FTIR) spectroscopy has been widely studied as a non-invasive optical method for glucose sensing. It can directly examine the fundamental vibrational modes of glucose molecules in the mid-infrared region [1], [2], [9]. Unlike near-infrared spectroscopy, which depends on weak overtone and combination bands, FTIR detects strong and chemically specific absorption features related to glucose. This results in better selectivity and analytical accuracy [2], [10]. For biological applications, Attenuated Total Reflection FTIR (ATR-FTIR) is often used. It employs an evanescent wave created at the interface of a high-refractive-index crystal to probe the sample within a shallow depth of a few micrometers. This minimizes the effects of water absorption and allows measurements in biological fluids and tissues [4], [7].

Glucose shows distinct absorption bands in the mid-infrared fingerprint region, typically between 800 and 1200 cm^{-1}. Significant peaks occur around 1030–1045 cm^{-1}, 1080 cm^{-1}, and 1110–1150 cm^{-1}. These correspond to C–O stretching, C–C stretching, and C–O–H bending vibrations [2], [4], [7]. These absorption features strongly correlate with glucose concentration in aqueous solutions and blood analogs, forming the basis for quantitative glucose estimation using FTIR spectroscopy. However, overlapping absorptions from water, proteins, and lipids in biological samples require careful signal processing techniques to accurately isolate glucose-specific spectral information [7], [13].

To tackle these challenges, FTIR-based glucose sensing systems often incorporate chemometric and multivariate analysis methods. Principal Component Analysis (PCA) is commonly used for dimensionality reduction and exploratory analysis. It helps identify spectral variance linked to glucose concentration changes [7], [13]. Partial Least Squares (PLS) regression is the most frequently used calibration technique. It maximizes the covariance between spectral features and reference glucose values, resulting in high prediction accuracy and reliability [7], [10]. Principal Component Regression (PCR) has also been explored, but studies show that PLS typically performs better for glucose estimation [10]. Preprocessing steps like baseline correction, normalization, and smoothing improve model stability and predictive power [7].

Compared to other optical glucose sensing techniques, such as Raman spectroscopy and near-infrared spectroscopy, FTIR has several benefits. These include higher chemical specificity, label-free operation, and good compatibility with multivariate modeling approaches [2], [9], [10]. While Raman spectroscopy allows for deeper tissue penetration and NIR techniques can enable compact device design, FTIR's direct access to fundamental vibrational modes offers better molecular selectivity and spectral clarity [3], [11], [14]. Key studies show that ATR-FTIR, when paired with strong chemometric models, can provide reliable glucose estimates under controlled situations. It also aligns well with reference measurements, as measured by established clinical accuracy metrics like the Clarke Error Grid [4], [6], [7]. Despite issues related to penetration depth and physiological variability, ongoing research highlights that improvements in sensor design, data integration, and signal processing could further boost the clinical use of FTIR-based non-invasive glucose monitoring systems [8], [15], [17].

C. Bio-Impedance Spectroscopy for Glucose Sensing

Bio-Impedance Spectroscopy (BIS) is an electrical sensing technique that analyzes biological tissues by measuring their response to an applied alternating current across various frequencies. The electrical impedance of tissue depends on its resistive and capacitive components. These components come from ionic conduction in extracellular and intracellular fluids, as well as the capacitive behavior of cell membranes. When an alternating current is applied, low frequencies mainly probe extracellular pathways. In contrast, higher frequencies penetrate cell membranes, allowing access to intracellular properties. This frequency-dependent behavior is the foundation of BIS and helps distinguish different tissue compartments.

Glucose concentration indirectly affects tissue electrical properties by changing osmotic balance, ionic concentration, and fluid distribution within and between tissue compartments. Changes in blood or interstitial glucose levels can cause noticeable variations in tissue conductivity and permittivity. These changes often occur due to shifts in electrolyte concentration and the effects of cell membrane polarization.

As glucose levels increase, shifts in extracellular fluid volume and dielectric properties influence impedance measurements. This enables a correlation between impedance parameters and glucose concentration. However, these effects are subtle and significantly affected by other physiological factors like hydration, temperature, blood flow, and tissue composition.

Multi-frequency BIS is often used to improve sensitivity and specificity. By collecting impedance spectra across a broad frequency range, compartmental models can estimate extracellular and intracellular contributions to total tissue impedance separately. These models enhance glucose correlation by isolating changes caused by glucose from other unrelated physiological variations. Additionally, BIS is being explored as part of multi-sensor and data-fusion systems, where impedance data is combined with optical or physiological measurements to boost glucose estimation accuracy.

BIS has several advantages. It operates non-invasively, consumes low power, has simple instrumentation, and is suitable for wearable and continuous monitoring applications. However, it has major limitations. These include low glucose specificity, sensitivity to physiological variability, effects from the electrode-skin interface, and calibration drift over time. As a result, BIS alone has not been accurate enough for clinical glucose monitoring. Current literature suggests that BIS works best as a complementary method within hybrid sensing systems rather than as a standalone glucose sensing technique.

D. Multimodal Approaches in Non-Invasive Glucose Monitoring (NIGM)

The ongoing challenges with single-modality non-invasive glucose monitoring, including low specificity, physiological variability, and limited reliability, have driven the development of multimodal sensing systems [1], [9], [13]. Individual techniques often capture only partial or indirect information about glucose levels, making them vulnerable to factors like hydration, temperature, tissue differences, and motion artifacts. Multimodal NIGM systems aim to address these issues by combining different sensing methods, which improves sensitivity, specificity, and overall prediction accuracy [8], [9], [17].

One prominent multimodal strategy combines FTIR and Raman spectroscopy. FTIR spectroscopy achieves high chemical specificity by probing the fundamental vibrational modes of glucose in the mid-infrared region. Meanwhile, Raman spectroscopy provides molecular identification with minimal interference from water absorption [2], [3], [7], [11]. By integrating the strong glucose absorption features of FTIR with the resistance to water-related artifacts of Raman, multimodal optical systems can deliver more reliable glucose estimates than either method alone [7], [9], [14]. Studies have shown that combining FTIR and Raman spectral features enhances calibration reliability and decreases prediction errors in glucose estimation models [7].

Another important multimodal approach involves combining FTIR spectroscopy with bio-impedance spectroscopy (BIS). FTIR provides chemically specific information about glucose concentration, while BIS measures changes in tissue electrical properties that glucose affects indirectly through osmotic and ionic effects, especially in extracellular spaces [9], [10], [15]. The complementary aspects of these methods allow FTIR to make up for the low specificity of BIS, while BIS adds sensitivity to physiological changes that do not show up in optical spectra. These hybrid systems are particularly promising for wearable and continuous monitoring applications [8], [17].

The advantages of multimodal systems come from the combined strengths of the techniques involved. FTIR spectroscopy supplies high molecular specificity through fundamental vibrational absorption bands. Raman spectroscopy reduces water interference and provides clear molecular fingerprints. BIS detects changes in extracellular fluid and conductivity linked to variations in glucose levels [3], [9], [11], [15]. By merging data from multiple modalities, multimodal NIGM systems can more effectively distinguish glucose-related signals from other physiological variations.

Early multimodal studies, especially those that involved multi-sensor data fusion, have reported greater accuracy in predicting glucose levels than single-modality methods [8]. These studies showed that integrating data from different sensors using multivariate analysis or machine learning techniques boosts reliability and lessens calibration drift. Recent reviews and workshops highlight that multimodal sensing, together with improved signal processing and data fusion strategies, is essential for developing clinically viable non-invasive glucose monitoring systems [9], [16], [17].

III. COMPARISON OF TECHNIQUES

Non-invasive glucose monitoring techniques involve trade-offs between molecular specificity, robustness, and real-time usability. Optical methods such as Fourier Transform Infrared (FTIR) and Raman spectroscopy directly measure glucose's molecular signatures, giving them higher specificity than electrical approaches. However, FTIR is limited by strong water absorption and high sensitivity to environmental conditions, which affects measurement stability.

Raman spectroscopy, while less affected by water, suffers from weak signal intensity and interference from fluorescence, making reliable detection challenging in practical scenarios.

On the other hand, bio-impedance spectroscopy (BIS) supports continuous and wearable glucose monitoring but lacks specificity because its measurements are influenced by individual physiological variations rather than glucose alone. To overcome the limitations of single techniques, multimodal systems combine complementary methods, such as integrating FTIR's molecular specificity with Raman's improved performance in wet environments or BIS's responsiveness to extracellular glucose changes. Research consistently indicates that these hybrid approaches provide improved accuracy, robustness, and reliability, making multimodal systems the most promising solution for effective non-invasive glucose monitoring

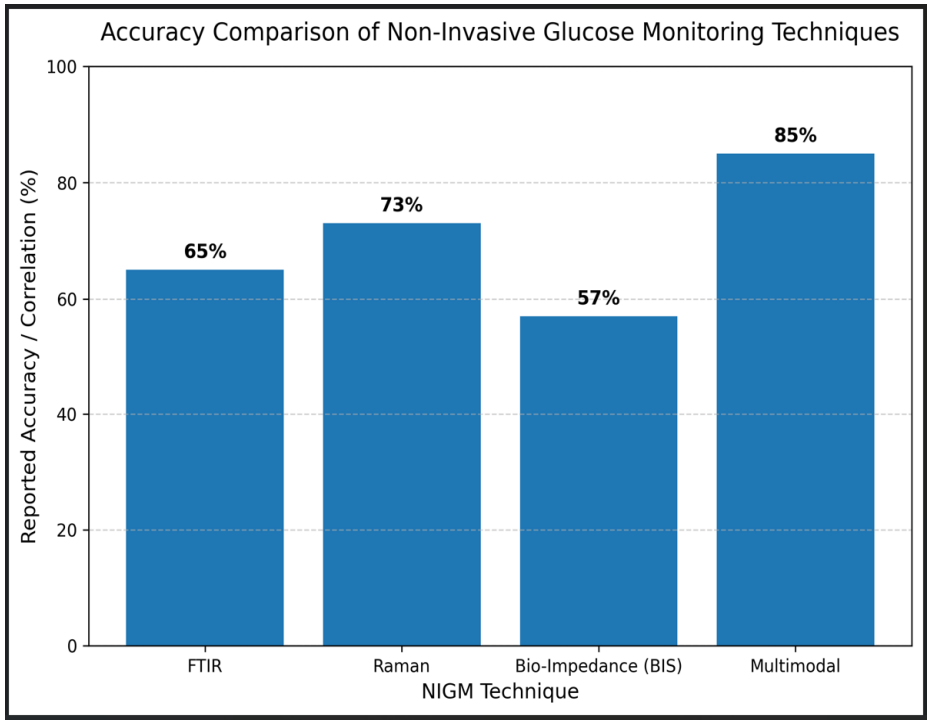


Figure.3.1. Accuracy Comparison of Non-Invasive Glucose Monitoring Techniques

Table No.3.1.Comparison Of Techniques.

Technique	Principle	Advantages	Limitations
FTIR (ATR-FTIR)	Mid-infrared absorption of glucose molecular bonds	High molecular specificity; label-free measurement	Strong water absorption; sensitivity to skin and environmental variations; requires chemometric modeling
Raman Spectroscopy	Inelastic light scattering providing molecular fingerprint	Inelastic light scattering providing molecular fingerprint	Weak Raman signal; fluorescence background
Bio-Impedance Spectroscopy (BIS)	Changes in tissue conductivity and permittivity with glucose	Real-time response; wearable-friendly	Low specificity; affected by hydration and temperature
Multimodal (FTIR + Raman / BIS)	Data fusion of complementary sensing modalities	Improved robustness and accuracy; reduced interference	Increased system complexity; advanced modeling required

IV. KEY FINDINGS FROM LITERATURE

FTIR-based non-invasive glucose sensing shows high molecular specificity for detecting glucose. However, its performance is significantly impacted by water absorption and skin-related interference.

Raman spectroscopy effectively complements FTIR by providing clear molecular fingerprints, but its practical use is limited by weak signal intensity and interference from fluorescence.

Bio-impedance spectroscopy allows for real-time monitoring and is suitable for wearable devices. However, it has low specificity because it is sensitive to changes in the body, like hydration and temperature.

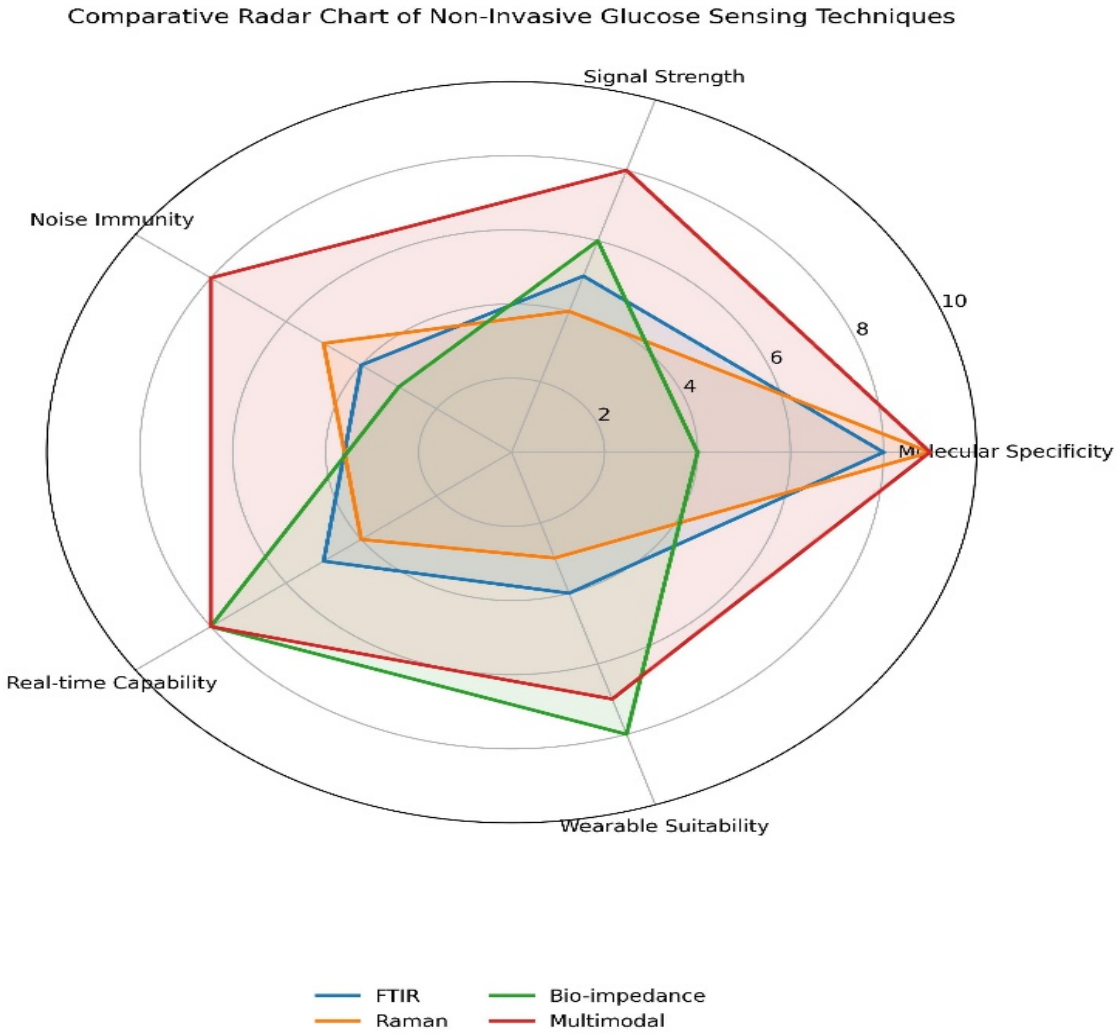


Figure.4.1. comparative Radar Chart of Non-invassive Glucose Sensing Techniques

Multimodal sensing approaches, which combine optical and electrical methods, consistently demonstrate better correlation with invasive glucose measurements. They also show improved durability and less vulnerability to the weaknesses of single methods.

Data fusion and chemometric modeling techniques are key for accurate non-invasive glucose estimation. They help in effectively extracting glucose-related information from complex physiological signals.

V. RESEARCH GAP

Single-modality non-invasive glucose monitoring systems such as FTIR, Raman spectroscopy, and bio-impedance suffer from inherent limitations, including sensitivity to environmental conditions, weak signal strength, and low glucose specificity. These challenges reduce their clinical reliability, especially when used independently.

Although some studies report encouraging results, current solutions still fail to deliver consistent real-time, continuous, and highly accurate glucose measurements, particularly under varying physiological and environmental conditions.

Multimodal systems offer a promising direction by integrating FTIR with complementary optical or electrical techniques to overcome the shortcomings of individual methods. However, robust and practically deployable multimodal systems are still limited. A major research gap lies in calibration and personalization, as variations in skin properties, hydration levels, tissue composition, and individual metabolism significantly impact measurement accuracy. Addressing these factors is essential for developing reliable and widely applicable non-invasive glucose monitoring technologies.

AIM - This research aims to create a non-invasive glucose sensing system that combines FTIR spectroscopy with other methods like Raman spectroscopy and/or bio-impedance. The goal is to improve the accuracy, reliability, and robustness of glucose predictions compared to using just one method.

Objectives

- To acquire and analyze glucose-specific spectral signatures using Mid-Infrared FTIR and Raman (including SERS) spectroscopy.
- To develop preprocessing and calibration models for accurate glucose concentration prediction.
- To compare the performance of FTIR, Raman, and combined (FTIR + Raman/BIS) approaches for non-invasive glucose monitoring.

To validate the system's accuracy against standard invasive glucose measurement methods.

VI. FUTURE PERSPECTIVES

- Integrating wearable devices and IoT platforms can enable continuous, real-time, non-invasive glucose monitoring. This helps with remote health tracking and improves diabetes management.
- Using machine learning and deep learning models for combining different types of data can greatly improve glucose prediction accuracy and how well the system adjusts to different body conditions.
- Personalized calibration strategies will be vital. They need to account for differences between individuals and within the same individual over time. This will boost long-term reliability and performance for each user.
- For clinical use and commercialization, we must tackle challenges like getting regulatory approval, ensuring long-term stability, maintaining user comfort, being cost-effective, and validating the system on a large scale.

VII. CONCLUSION

Non-invasive glucose monitoring remains one of the most challenging yet impactful goals in diabetes management. This review highlights that while individual sensing techniques such as FTIR spectroscopy, Raman spectroscopy, and bio-impedance spectroscopy each offer valuable insights into glucose-related physiological changes, none are sufficient on their own to deliver consistent, clinically reliable performance under real-world conditions. Optical methods provide high molecular specificity but are limited by tissue interference, weak signal strength, and environmental sensitivity, whereas electrical methods enable continuous monitoring but lack glucose specificity and are strongly influenced by physiological variability.

The literature consistently demonstrates that multimodal non-invasive glucose monitoring systems offer a superior solution by integrating complementary sensing modalities. In particular, combining FTIR's strong molecular selectivity with Raman spectroscopy's reduced water interference or bio-impedance's sensitivity to extracellular physiological changes significantly enhances accuracy, robustness, and reliability. When supported by advanced chemometric modeling and data fusion techniques, these hybrid systems show improved correlation with invasive reference measurements and reduced susceptibility to calibration drift and external disturbances.

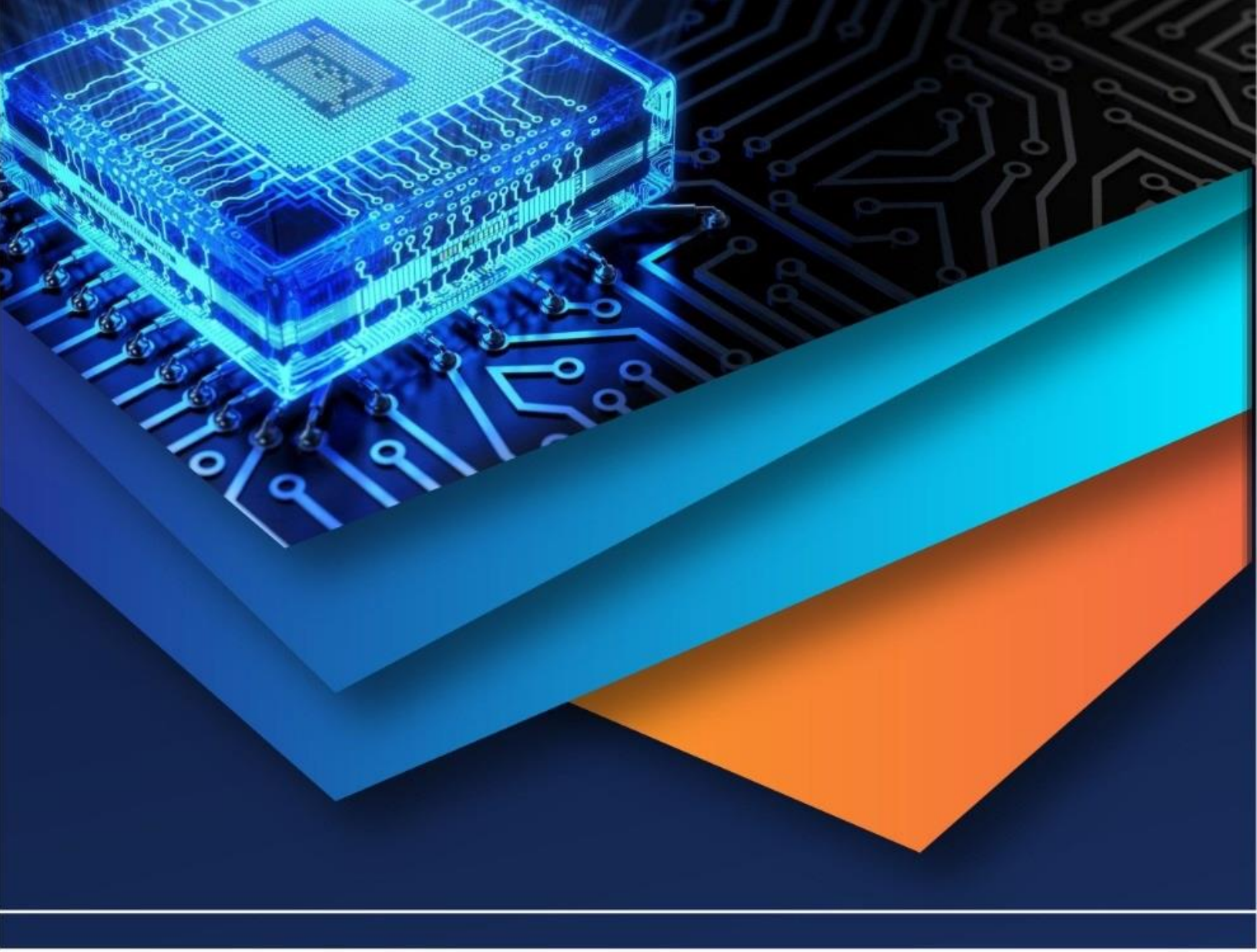
Despite these advancements, important challenges remain, including personalized calibration, long-term stability, wearable system integration, and large-scale clinical validation. Addressing these issues will be critical for translating multimodal NIGM technologies from laboratory research to practical healthcare solutions. Overall, this review concludes that integrated multimodal sensing, coupled with intelligent data processing, represents the most promising pathway toward accurate, continuous, and patient-friendly non-invasive glucose monitoring, with strong potential to transform future diabetes care.

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