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A Review of Non-Invasive Blood Glucose Monitoring Using Near-Infrared NIR Spectroscopy - Technologies and Challenges

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Abstract

Diabetes mellitus is rapidly increasing worldwide, creating an urgent demand for continuous, accurate, and user-friendly glucose monitoring methods. Conventional invasive self-monitoring of blood glucose (SMBG), although widely adopted, still presents several limitations, including pain, inconvenience, high consumable costs, and the inability to support continuous monitoring. In this context, non-invasive glucose monitoring technologies based on near-infrared (NIR) spectroscopy have attracted significant attention from the research community. The operating principle relies on the absorption and scattering of NIR light interacting with characteristic chemical bonds of glucose molecules in biological tissues. This review presents the theoretical foundations of NIR spectroscopy, including transmission and reflectance sensor configurations, as well as emerging trends in integrating NIR photoplethysmography (PPG). Furthermore, the roles of signal processing techniques, nonlinear feature extraction, and machine learning models in modeling the relationship between optical signals and glucose concentration are comprehensively analyzed. Alongside its promising application potential, this paper also discusses remaining challenges such as motion artifacts, inter-individual physiological variability, and the requirement for personalized calibration.

Keywords: Machine learning, near-infrared spectroscopy, non-invasive glucose monitoring, optical sensing, photoplethysmography.

1. Introduction

1.1. Global Burden of Diabetes Mellitus

Diabetes mellitus is currently one of the fastest-growing chronic diseases worldwide, posing a major challenge to healthcare systems and socio-economic development. The disease is characterized by chronic hyperglycemia resulting from metabolic disorders and remains incurable [1]. The increasing prevalence of obesity, sedentary lifestyles, excessive energy intake, and population aging has significantly contributed to the rapid rise of type 2 diabetes over recent decades [2]. It is estimated that approximately 537 million people are living with diabetes globally, and this number is projected to increase substantially in the coming years [3–5].

Beyond its high prevalence, diabetes is associated with severe long-term complications if blood glucose levels are not effectively controlled. Prolonged hyperglycemia can lead to diabetic retinopathy, nephropathy, neuropathy, and, most critically, cardiovascular events, which remain the leading cause of mortality among diabetic patients [4, 6, 7]. These complications significantly impair quality of life and impose a substantial economic burden due to long-term treatment and care.

In this context, frequent and continuous glucose monitoring (Continuous Glucose Monitoring – CGM) plays a central role in diabetes management by enabling early detection of abnormal glucose fluctuations and facilitating the optimization of therapeutic regimens [8–10]. However, conventional glucose monitoring methods based on blood sampling remain painful, inconvenient, and costly [11, 12]. This situation highlights the urgent need for non-invasive, accurate, and user-friendly glucose monitoring technologies to reduce patient burden and improve long-term disease management outcomes [13, 14].

1.2. Limitations of Invasive Glucose Monitoring Methods

Traditional blood glucose monitoring methods rely on repeated finger-prick capillary blood sampling several times per day, which causes pain, discomfort, and carries a potential risk of infection at the puncture site [15]. Although these methods provide accurate point measurements, they only offer discrete glucose values and fail to capture continuous glucose dynamics throughout the day, which are critical for effective glycemic control [16]. The need for frequent measurements also negatively affects patient adherence and compliance with treatment protocols [17].

Current continuous glucose monitoring systems have improved the ability to track glucose dynamics in real time; however, they remain minimally invasive, as they require the insertion of sensors into the subcutaneous tissue. These systems are often associated

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with high costs and potential complications related to sensor implantation and maintenance [18, 19]. Such limitations underscore the necessity for fully non-invasive, safe, and convenient glucose monitoring technologies to enhance long-term diabetes management and patient acceptance [20, 21].

1.3. Trends in Non-Invasive Glucose Monitoring Technologies

The growing demand for continuous glucose monitoring has stimulated extensive research into non-invasive glucose sensing approaches based on various physical and biochemical principles. Existing approaches can be broadly classified into optical methods (e.g., near-infrared spectroscopy, Raman spectroscopy, and polarimetry), microwave-based techniques, thermal metabolic methods, electrochemical sensing, and bio-impedance measurements. These approaches exploit glucose-induced variations in the optical, dielectric, thermal, or electrical properties of biological tissues [4,22,23].

Table 1 provides a comparative overview of major non-invasive glucose monitoring technologies in terms of sensing principles, application environments, advantages, and technical limitations, thereby highlighting differences in their clinical potential.

Among these approaches, near-infrared (NIR) spectroscopy has emerged as a particularly promising technique due to its ability to safely penetrate biological tissues and its potential for integration into wearable devices [22, 24]. NIR spectroscopy operates within the wavelength range of 700–2500 nm and analyzes light absorption and scattering resulting from interactions with chemical bonds associated with glucose molecules in biological tissues [16, 22]. The integration of NIR sensors with photoplethysmography (PPG) signals and machine learning algorithms has significantly improved prediction performance. Nevertheless, challenges related to glucose specificity and clinical reliability remain and continue to be the focus of ongoing research efforts [25].

Table 1. Comparison of Non-Invasive Glucose Monitoring Technologies

Technology/ Method	Measurement Principle	Research Stage	Measurement Medium/Site	RMSE (mg/dL)	MARD (%)	Number of Subjects	Level of Clinical Validation	Main Advantages	Main Limitations	References
Near-Infrared (NIR) Spectroscopy	Measurement of overtone and combination absorption of O–H and C–H bonds within the 700–2500 nm spectral range	In vitro, in vivo	Serum, standard solutions, skin (finger, forearm)	15–20	15–20	20–100	Research / Experimental Stage	Safe, non-ionizing, suitable for wearable integration	Strong spectral overlap with water; high tissue scattering	[1], [2], [6], [8], [24]
Mid-Infrared (MIR) Spectroscopy	Measurement of fundamental vibrational absorption of glucose molecules	In vitro, preclinical	Biological samples	~10–15	~10–15	<20	Preclinical Stage	High molecular specificity	Strong water absorption; limited tissue penetration	[1]
Raman Spectroscopy	Analysis of characteristic Raman scattering signatures of glucose	In vitro, experimental	Skin, solutions	12–18	12–20	20–30	Experimental Stage	Direct molecular fingerprinting of glucose	Weak signal intensity; high fluorescence interference	[3], [18]
Enhanced Optical Sensors	Optimized optical configuration combined with advanced signal processing	In vivo prototype	Fingertip	~12–15	~12–15	~30	Experimental Stage	Improved accuracy compared with conventional NIR systems	Requires individual calibration	[4]

Microwave Sensors (2.4 GHz)	Detection of changes in tissue dielectric properties correlated with glucose concentration	Prototype	Through biological tissue	15–25	~18–25	~20	Experimental Stage	Independent of optical water absorption	Sensitive to temperature and tissue heterogeneity	[20], [21]
PPG-based Glucose Estimation	Extraction of pulse waveform features followed by machine learning regression	In vivo	Skin, peripheral capillaries	10–15	10–18	50–150	Research Stage	Wearable integration; low cost	Indirect relationship; highly data-dependent	[10], [11]
Multi-wavelength PPG + SVM/AI	Combination of multiple optical wavelengths with machine learning models	Experimental studies	Skin	~10–14	~10–15	~30	Experimental Stage	Higher accuracy than single-wavelength PPG	Requires large training datasets	[12]
Nanozyme-based Colorimetric Biosensors	Nanozyme-catalyzed colorimetric reactions with quantitative analysis algorithms	In vitro	Biological samples	<10	<10	<20	Preclinical Stage	High sensitivity	Difficult to integrate into wearable platforms	[15]
Electrochemical Biosensors / Next-generation CGM	Enzyme-based electrochemical biosensing of glucose	Clinical use	Interstitial fluid	8–10	8–10	>1000	Clinical Stage	High accuracy	Minimally invasive	[13], [25]

Quantitative analysis indicates that conventional optical approaches, such as near-infrared (NIR) spectroscopy, remain constrained by the "water barrier," resulting in relatively high MARD values (~15%–20%). However, the integration of multi-wavelength PPG with machine learning models has demonstrated a notable reduction in error, achieving MARD levels of approximately 10%–15%, thereby approaching the lower bound of initial clinical acceptability.

Despite this progress, a performance gap persists when compared to current continuous glucose monitoring (CGM) systems (~8%–10%). Nevertheless, the convergence of multi-wavelength sensing, advanced signal processing, and machine learning is increasingly recognized as the most promising pathway toward bridging this gap in future non-invasive glucose monitoring technologies.

2. Principles of Near-Infrared (NIR) Spectroscopy

2.1. Spectral Region of Near-Infrared (NIR)

Near-infrared (NIR) spectroscopy covers the wavelength range from approximately 700 to 2500 nm, encompassing absorption bands arising from overtone and combination vibrations of O–H and C–H bonds in biological molecules [15]. However, within human tissue, the absorption contribution of glucose in this spectral region is extremely weak, accounting for less than 0.1% of the total absorption, while water remains the dominant absorbing constituent. This strong spectral overlap significantly degrades the signal-to-noise ratio and complicates glucose quantification [26]. Consequently, NIR-based glucose sensing systems require advanced signal processing techniques and multivariate modeling approaches to effectively extract glucose-related information from complex spectral backgrounds [15].

The wavelength range of 700–1100 nm, often referred to as the optical window, is preferred for non-invasive measurements due to its relatively low background absorption and superior tissue penetration capability [7, 27]. In contrast, the 1300–2500 nm region contains first-overtone absorption bands directly associated with the O–H and C–H groups of glucose, offering improved spectral specificity [28]. Although the mid-infrared region exhibits stronger absorption features, its limited tissue penetration renders it less suitable for transcutaneous glucose measurements [29, 30].

Therefore, short-wavelength NIR remains the most practical spectral range for non-invasive glucose

monitoring, albeit with stringent requirements for system sensitivity and spectral resolution [17,31].

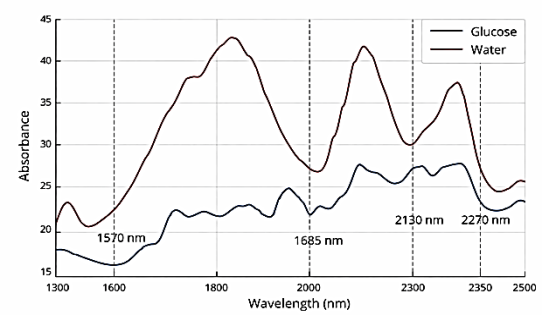

Fig. 1. Absorption spectra of glucose and water in the near-infrared (NIR) region

The NIR spectrum indicates that glucose exhibits characteristic absorption bands around 1600–1700 nm and 2100–2300 nm; however, these features are relatively weak and are strongly overlapped by water, which is the dominant constituent of biological tissues. This pronounced spectral overlap constitutes a fundamental challenge for non-invasive glucose monitoring. Overcoming the "water barrier" in non-invasive blood glucose monitoring using PPG combined with near-infrared (NIR) spectroscopy remains a highly complex challenge. This difficulty arises from the inherently weak absorption signature of glucose, which is significantly overshadowed by the strong and time-varying absorption background of water and biological tissues. To address this limitation, modern systems typically employ multi-wavelength configurations incorporating both measurement and reference channels to effectively characterize the water background. These approaches are further enhanced through the application of AC/DC decomposition, logarithmic ratio techniques, and multi-wavelength differential methods to suppress common-mode absorption components. In addition, spectral preprocessing techniques, such as standard normal variate (SNV) and derivative spectroscopy, together with multivariate calibration methods (e.g., partial least squares (PLS) regression and deep learning models), are widely adopted to extract glucose-specific signals from the dominant water background within the feature space [17]. Furthermore, recent advances in integrated multi-channel spectrometers have significantly improved spectral resolution and signal discrimination capabilities under high-noise conditions [31].

2.2. Interaction Mechanisms Between NIR Radiation and Biological Tissue

When near-infrared radiation propagates through biological tissue, it is simultaneously affected by absorption, scattering, reflection, and transmission, resulting in a complex optical signal that requires careful interpretation.

In terms of absorption, molecular bonds such as O–H, C–H, and N–H present in biological tissues give rise to overtone absorption bands in the NIR region [32]. Among these constituents, water and hemoglobin are the primary absorbers, whereas the absorption contribution of glucose is relatively weak and strongly overlapped by other tissue components [33]. Nevertheless, the characteristic vibrational modes of glucose-related O–H and C–H bonds still provide a theoretical basis for glucose quantification in tissue [34].

Light scattering is strongly dependent on the microstructural properties of biological tissues and the wavelength of incident radiation, resulting in altered photon propagation paths and interference with absorption measurements [8]. In addition, physiological factors such as blood flow and temperature significantly influence both scattering and absorption characteristics, thereby increasing the complexity of optical measurements [2]. In particular, temperature variations can induce signal drift by affecting tissue perfusion as well as the optical properties of sensing components.To mitigate these effects, modern NIR-based systems typically incorporate temperature compensation strategies. These include the integration of temperature sensors at the hardware level to monitor skin or ambient temperature, combined with temperature correction algorithms during signal processing, thereby improving measurement stability and overall accuracy.

The penetration capability of NIR radiation allows interaction with deeper tissue layers, including interstitial fluid, which exhibits a strong correlation with blood glucose concentration [35]. However, due to spectral overlap with water and other metabolites, accurate glucose estimation requires optimal wavelength selection and the application of multivariate and machine learning-based algorithms to enhance specificity and robustness [12, 33, 36].

2.3. Modified Beer–Lambert Law

The classical Beer–Lambert law assumes a homogeneous, non-scattering medium and is therefore not directly applicable to biological tissues, where strong scattering and structural heterogeneity dominate light propagation [37].

In a homogeneous, non-scattering medium, the attenuation of light intensity is described by:

$$\mathrm{I} = I_0 e^{-\alpha L} \tag{1}$$

or equivalently, in logarithmic form:

$$\mathrm{A} = \ln\left(\frac{I_0}{I}\right) = \alpha L \tag{2}$$

In there:

I_0: denotes the incident light intensity

I: is the transmitted light intensity

α : is the absorption coefficient

L: represents the optical path length

A: is the absorbance.

For a medium containing multiple absorbing species, the absorbance can be expressed as:

$$A = \sum_i \varepsilon_i c_i L \quad (3)$$

In there:

ε_i: is the molar absorption coefficient of the i-th absorber

c_i: is its concentration.

This formulation is valid for homogeneous, non-scattering media such as standard solutions under controlled laboratory conditions.

To address the effects of scattering in biological tissue, the Modified Beer–Lambert Law (MBLL) introduces an effective optical path length to account for photon pathlength elongation caused by multiple scattering events [9]. The MBLL is expressed as:

$$A = \ln\left(\frac{I_0}{I}\right) = \varepsilon c L_{eff} + G \quad (4)$$

or $$A = \varepsilon c.L.DPF + G \quad (5)$$

In there:

$L_{eff} = L.DPF$

DPF: pathlength factor accounting for scattering-induced pathlength elongation

G: epresents baseline attenuation due to tissue scattering and structural heterogeneity

$\varepsilon c.L.DPF$: Concentration-dependent absorption component

Fig. 2 illustrates photon propagation in biological tissue, where multiple scattering events elongate the effective optical path length and thereby violate the linear assumptions of the classical Beer–Lambert model.

In biological tissues, an increase in glucose concentration alters the refractive index of extracellular fluid, thereby affecting the scattering coefficient and anisotropy of the medium [8, 16]. In addition, glucose-induced changes in cell size and extracellular matrix structure further modify the overall optical properties of tissue [27]. As a result, quantitative models for non-invasive glucose monitoring must simultaneously consider both absorption and scattering effects to ensure reliable accuracy.

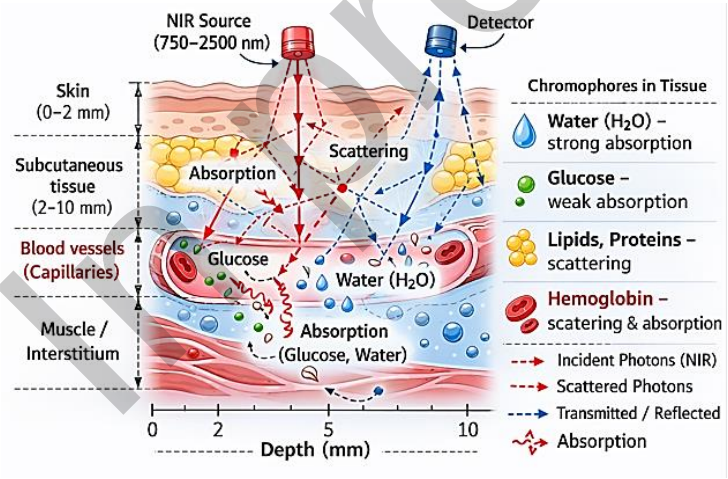

Fig. 2. Schematic illustration of photon propagation in biological tissue

3. NIR Sensors for Glucose Measurement

3.1. Transmission Configuration of NIR Sensors

In the transmission configuration of near-infrared spectroscopy, the light source and photodetector are positioned on opposite sides of the biological tissue, enabling direct measurement of the light intensity after it has traversed the tissue [38]. This configuration is particularly suitable for thin tissue sites, such as the fingertip or earlobe, where NIR radiation can penetrate the tissue and provide integrated information on its optical absorption properties [39].

Quantitative estimation is based on the attenuation of transmitted light intensity at selected wavelengths, where variations in glucose concentration lead to changes in the effective absorption coefficient of the tissue [8, 40]. Several systems employ multi-wavelength illumination, for example at 450, 900, 1350, and 1800 nm, to enhance discrimination of glucose-related signals within a complex spectral environment [4]. In addition, compensation algorithms are commonly incorporated to mitigate the influence of temperature, humidity, and other physiological factors [26].

Despite these advantages, the applicability of the transmission mode is constrained by strong absorption from water and endogenous chromophores, which

reduces the signal-to-noise ratio when probing deeper tissue layers [41].

3.2. Reflectance Configuration of NIR Sensors

In the reflectance configuration, the NIR light source and photodetector are placed on the same side of the skin, collecting light that has been scattered and reflected back from subsurface tissue layers [23]. This configuration is well suited for measurement sites such as the finger, forearm, or oral mucosa, where a transmission setup is impractical [9, 23].

The reflected signal reflects changes in the refractive index and scattering properties of tissue as glucose concentration in the interstitial fluid varies [7]. Systems operating at wavelengths around 940 nm have demonstrated the ability to detect glucose-related variations through analysis of reflected light intensity [22]. However, reflectance-based measurements are inherently sensitive to blood perfusion, skin temperature, and surface moisture, necessitating the use of multivariate correction and signal processing algorithms to ensure robustness and accuracy [42].

3.3. Comparison Between Transmission and Reflectance Configurations

The transmission configuration generally provides more stable signals and reduced sensitivity to surface-related artifacts, as light propagates through the entire tissue volume between the emitter and detector. However, its applicability is limited to thin tissue sites, such as the fingertip or earlobe [43].

In contrast, the reflectance configuration offers greater flexibility in measurement location and is more amenable to integration into wearable devices, although the acquired signals are more susceptible to variations in blood flow, temperature, and skin–sensor contact conditions [22, 44]. Table 2 summarizes the key differences between transmission and reflectance configurations in terms of signal acquisition principles, measurement sites, advantages, and technical limitations. Fig. 3 provides a schematic comparison of photon propagation paths and tissue interaction volumes for the two configurations.

Consequently, the choice of configuration depends on the intended application and the physiological characteristics of the target population. Current research trends increasingly focus on hybrid configurations or wearable-integrated sensor designs to balance accuracy, usability, and clinical applicability [10, 38].

Table 2. Comparison of Transmission and Reflectance

Criteria	Transmission Mode	Reflectance Mode	References
Measurement principle	Measurement of light intensity transmitted through biological tissue; the signal is detected on the opposite side of the light source	Measurement of backscattered and reflected light collected on the same side as the light source	[22], [44]
Sensor configuration	LED emitter and photodetector positioned opposite each other (e.g., fingertip, earlobe)	LED emitter and photodetector positioned on the same side with a small separation distance (typically a few millimeters)	[22], [38]
Optical penetration depth	Greater penetration depth; light traverses the full thickness of the tissue	Shallower penetration; interaction mainly with superficial tissue layers and shallow capillaries	[44]
Signal quality	Strong signal with higher signal-to-noise ratio (SNR) when applied to suitable tissue sites	More sensitive to scattering noise and motion artifacts	[10], [44]
Typical measurement sites	Fingertip, earlobe (thin tissue, minimal bone interference)	Wrist, forearm, forehead	[22], [38]
Wearable integration	Limited due to the requirement for access to both sides of the tissue	Highly suitable for wearable devices (e.g., smartwatches, wristbands)	[10], [43]
Sensitivity to motion artifacts	Lower sensitivity when the sensor is properly fixed	Higher sensitivity due to motion and variations in contact pressure	[10], [44]
Application in PPG-based glucose monitoring	Less commonly used in modern wearable systems	Widely used in PPG and multi-wavelength optical sensors	[10], [43]
Main advantages	Well-defined optical path, reduced dependence on surface tissue properties	Compact design, flexible placement, easier commercialization	[22], [43]
Main limitations	Not applicable to thick tissue regions	Signal strongly dependent on tissue scattering and surface conditions	[44]

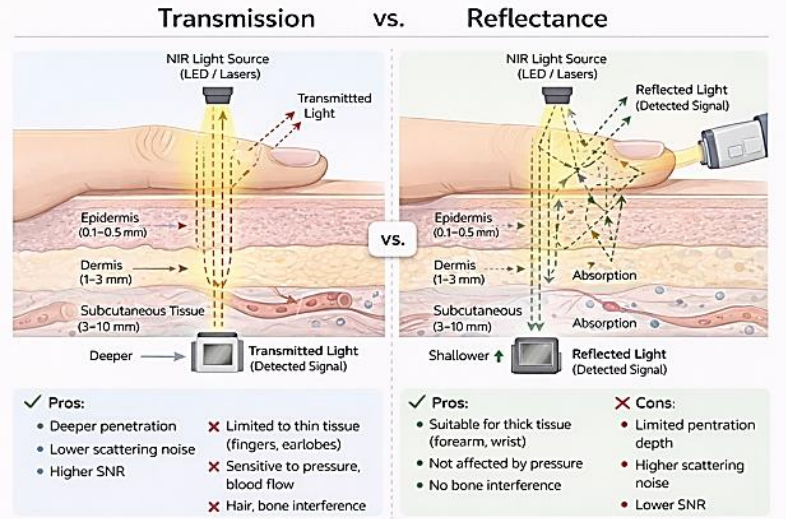

Fig. 3. Comparison Between Transmission and Reflectance Configurations

4. NIR–PPG and Artificial Intelligence for Glucose Prediction

4.1. Principles of PPG in Non-Invasive Glucose Monitoring

Photoplethysmography (PPG) is a non-invasive optical technique based on periodic variations in microvascular blood volume driven by the cardiac cycle. When red or near-infrared light illuminates biological tissue, the intensity of the reflected or transmitted light fluctuates synchronously with the heartbeat, generating a characteristic PPG signal [10].

In glucose monitoring, changes in glucose concentration can influence the optical properties of blood and surrounding tissue, thereby modulating the amplitude and morphology of the PPG waveform, particularly in the NIR spectral range [24, 45]. Although glucose-related effects are relatively subtle and are confounded by water absorption and limited penetration depth, the integration of NIR spectroscopy with PPG, together with advanced signal processing and machine learning algorithms, has demonstrated considerable potential for non-invasive glucose monitoring [10, 12, 28].

4.2. Signal Processing Pipeline for PPG-Based Glucose Estimation

The signal processing workflow for PPG-based glucose estimation typically follows a standardized pipeline, ranging from data acquisition to clinical performance evaluation. Fig. 4 illustrates an integrated NIR–PPG–ML pipeline, depicting the sequence from optical sensing to predictive modeling and clinical validation.

(1) PPG acquisition:

PPG signals are recorded using optical sensors (LED–photodiode pairs) placed on the skin, yielding rawtime-series data [46].

(2) Noise filtering:

Band-pass filtering is applied to suppress motion artifacts, electromagnetic interference, and out-of-band physiological components. Some studies additionally employ adaptive filtering or machine learning–based denoising to enhance robustness against motion noise [10, 24, 47].

(3) Baseline drift removal:

Low-frequency baseline wander caused by respiration, variations in contact pressure, or sensor displacement is removed using high-pass filtering, detrending, or asymmetric least squares (AsLS) methods, thereby preserving stable PPG pulse morphology [12, 48, 49].

(4) Signal segmentation:

The PPG signal is segmented into short windows (typically 5–8 s, possibly overlapping) to ensure sufficient cardiac cycles for feature extraction and compatibility with machine learning inputs. Low-quality segments are excluded based on spectral or physiological criteria [10, 50, 51].

(5) Glucose-related feature extraction:

Time-domain, frequency-domain, and nonlinear features–such as heart rate (HR/HRV), waveform morphology, wavelet coefficients, entropy measures, Teager–Kaiser energy, and autoregressive (AR) parameters–are extracted to serve as model inputs [10, 47, 52].

(6) Machine learning model training:

Regression or deep learning models, including SVR, Random Forest, XGBoost, and neural networks (CNN/LSTM), are trained using appropriate train/validation/test splits to mitigate overfitting and improve generalization [10, 53, 54].

(7) Clinical performance evaluation:

Beyond conventional error metrics (e.g., RMSE, mARD), clinical reliability is assessed using the Clarke Error Grid, which evaluates the safety and clinical relevance of prediction errors in therapeutic decision-making contexts [17, 55, 56].

4.3. Common Feature Groups for Glucose Estimation from PPG

(1) Time-domain features:

Time-domain features directly describe the waveform shape and amplitude of PPG signals using basic statistical measures (e.g., mean, standard deviation, peak-to-peak amplitude) and morphological parameters, thereby reflecting variations in blood flow and vascular characteristics [10]. Commonly used indices include peak-to-peak intervals for heart rate estimation and periodicity, pulse amplitude associated with pulsatile blood volume responses, and pulse transit time (PTT), which serves as an indirect indicator of arterial stiffness and blood pressure [10, 46, 57].

(2) Frequency-domain features:

Frequency-domain features are obtained using Fourier transform–based methods (or their variants) to analyze oscillatory components and the distribution of signal energy across frequency bands, helping to elucidate latent physiological processes within the signal [10]. Two widely used features are power spectral density (PSD), which quantifies energy within specific frequency ranges and identifies dominant components, and spectral entropy, which reflects the complexity and randomness of the signal [10, 58].

(3) Energy-based features:

Energy-based features quantify the intensity of signal activity and are often sensitive to subtle physiological variations [59]. The Kaiser–Teager Energy (KTE) operator is a nonlinear metric that tracks instantaneous energy and is useful for detecting small changes in PPG signals [60]. Logarithmic energy compresses the dynamic range and highlights subtle energy variations; these features can be extracted in the time–frequency domain or via wavelet analysis [61]. In addition, amplitude and phase features derived from FFT and instantaneous frequency measures from Hilbert–Huang transforms have also been explored in several studies [62].

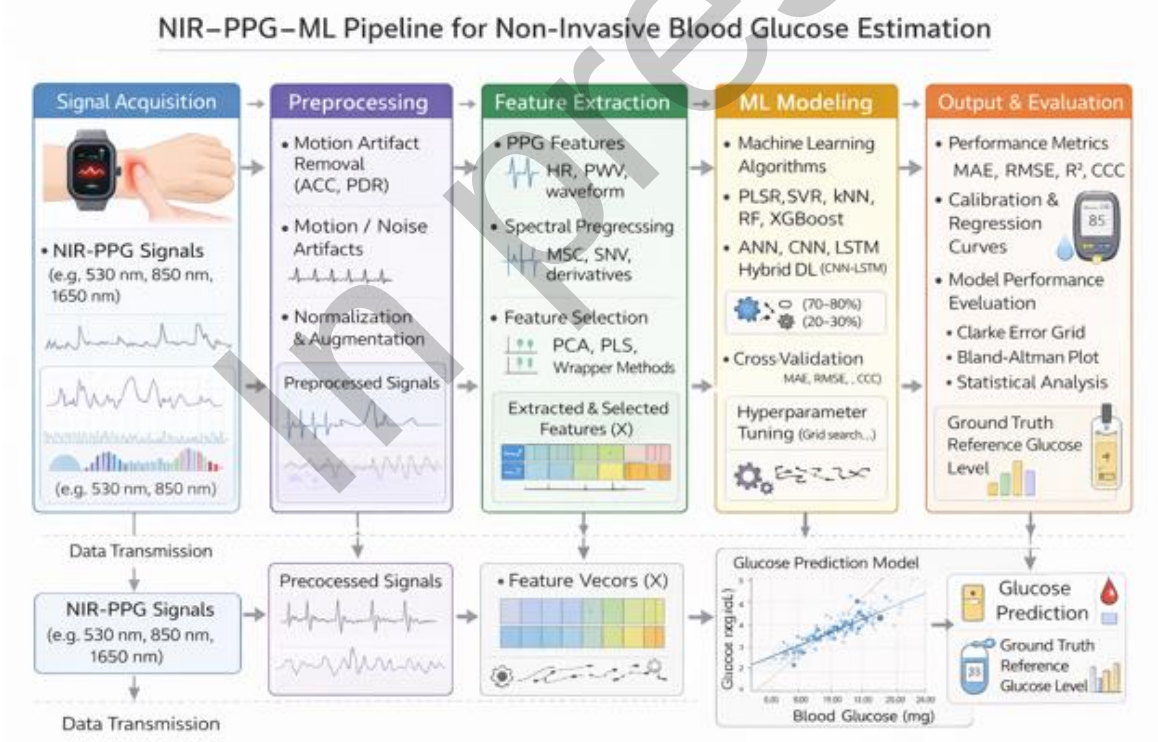

Fig. 4. NIR–PPG–ML signal processing pipeline

(4) Nonlinear features:

Nonlinear features aim to characterize the dynamics and complexity of signals beyond linear statistical measures and are particularly useful when signals are influenced by multiple interacting physiological factors [63]. Detrended fluctuation analysis (DFA) quantifies long-range correlations in time-series data, reflecting scale-dependent fluctuation structures [64]. Wavelet entropy evaluates multiscale irregularity and complexity derived from wavelet coefficients, making it well suited for non-stationary PPG signals [65].

5. Machine Learning Algorithms for PPG Analysis

Machine learning algorithms play a central role in modeling the nonlinear relationship between PPG-derived features and glucose concentration,

enabling the development of highly accurate prediction and classification systems [66]. Depending on data characteristics and application objectives, a wide range of approaches–from traditional linear models to advanced deep learning techniques–have been employed. Table 3 summarizes and compares machine learning algorithms commonly applied to PPG-based glucose estimation in terms of modeling principles, advantages, limitations, and data requirements.

Linear regression represents a fundamental approach for modeling the relationship between PPG features and the target variable; however, due to the inherently nonlinear nature of physiological signals, its performance is often limited [66, 67].

Random Forest and tree-based models such as LightGBM and XGBoost have demonstrated strong performance in handling high-dimensional and noisy data, owing to their ensemble learning mechanisms and ability to reduce overfitting [68, 69].

Support Vector Machine (SVM), particularly with a Gaussian (RBF) kernel, is capable of modeling complex nonlinear relationships and optimizing decision boundaries, making it suitable for both regression and classification tasks in PPG analysis [62, 70].

At a more advanced level, artificial neural networks (ANN/MLP) and deep learning architectures such as convolutional neural networks (CNNs) and recurrent neural networks (RNNs) can learn directly from raw PPG signals, automatically extracting hierarchical feature representations without the need for handcrafted feature engineering [71,72]. Deep learning approaches are especially advantageous for continuous monitoring systems, where signals exhibit dynamic temporal variations. However, these models typically require large, well-annotated datasets to achieve optimal performance and generalization capability [73].

Overall, the selection of an appropriate algorithm depends on factors such as dataset size, feature complexity, and clinical requirements, including prediction accuracy, generalization ability, and model interpretability.

Table 3. Comparison of Machine Learning Algorithms for PPG-Based Glucose Estimation

Algorithm	Nonlinear Modeling Capability	Data Requirement	Model Interpretability	Suitability for Wearable Systems	References
Linear Regression (LR)	Low	Low	High	Yes	[1], [22], [24]
Partial Least Squares Regression (PLSR)	Moderate	Moderate	Moderate-High	Yes	[1], [3], [16], [44]
Ridge/Lasso/Elastic Net	Moderate	Moderate	Moderate-High	Yes	[1], [22]
Support Vector Machine (SVR/SVM)	Moderate-High	Moderate	Moderate	Yes	[10], [22], [44]
k-Nearest Neighbors (kNN)	Moderate	Moderate	Moderate	Yes	[22], [24]
Decision Tree (DT)	Moderate	Moderate	High	Yes	[22], [10]
Random Forest (RF)	High	Moderate	Moderate	Yes	[10], [22], [40]
Gradient Boosting (XGBoost/LightGBM)	High	Moderate-High	Low–Moderate	Yes	[10], [40], [55]
Artificial Neural Network (ANN/MLP)	High	High	Low	Limited	[5], [22], [40]
Convolutional Neural Network (CNN)	Very High	High	Low	Limited	[10], [40], [55]
Recurrent Neural Network (LSTM/GRU)	Very High	High	Low	Limited	[10], [55]
CNN–LSTM / Hybrid DL	Very High	Very High	Low	Research-stage	[10], [40], [55]
TinyML / DL on-device	High	Moderate-High	Low	Yes (potential)	[10]

6. Comparative Performance Analysis of Previous Studies

Numerous studies have evaluated the performance of machine learning and deep learning algorithms in PPG signal analysis for the prediction of physiological parameters and the detection of pathological conditions, particularly in the context of cardiovascular and metabolic monitoring [20]. Overall, deep learning models have demonstrated clear advantages in directly exploiting raw signals and automatically learning complex feature representations that are difficult to capture using handcrafted approaches [74,75]. Table 4 summarizes recent studies that apply NIR–PPG combined with machine learning for glucose estimation, highlighting experimental design, dataset scale, employed algorithms, and performance evaluation metrics.

In particular, convolutional neural networks (CNNs) are capable of integrating feature extraction and classification within a unified architecture, enabling optimized data representations to be learned during training and achieving high performance when operating on large datasets [75, 76]. In several studies on atrial fibrillation detection from PPG signals, CNNs and deep neural networks (DNNs) have outperformed SVM-based methods in terms of area under the ROC curve (AUC) and the accuracy of probabilistic estimation [77].

In contrast, Random Forest and SVM-based methods remain widely adopted due to their robustness, ability to perform well on small datasets, and comparatively better model interpretability [58, 78]. SVM models are generally less prone to overfitting and demonstrate strong performance under limited data conditions; however, their performance tends to saturate as dataset size increases, whereas deep neural networks (DNNs) continue to improve by leveraging their capacity to learn increasingly complex nonlinear representations [79, 80].

Consequently, current research trends increasingly focus on the development of hybrid models that combine the strengths of traditional machine learning and deep learning approaches to achieve a balance between prediction accuracy, generalization capability, and practical deployability in clinical environments [58, 78].

Table 4: Summary of Recent NIR–PPG–Based Studies for Glucose Estimation

Authors	Year	Sensor	ML Model	Dataset (n)	RMSE	Clarke A+B	References
Castro-Pimentel *et al.*	2023	3λ PPG	SVM	50	18 mg/dL	95%	[12]
Chu *et al.*	2021	PPG	CNN	200	15 mg/dL	97%	[53]
Naresh *et al.*	2024	NIR	Random Forest	120	20 mg/dL	92%	[45]
Zeynali *et al.*	2025	PPG	Deep Learning (CNN/LSTM)	180	14 mg/dL	96%	[46]
Islam *et al.*	2021	Smartphone PPG	ML Regression	150	17 mg/dL	94%	[48]
Adıgüzel *et al.*	2024	PPG	Explainable AI	140	16 mg/dL	95%	[54]
Belfarsi *et al.*	2025	Spectroscopy	CNN	160	13 mg/dL	96%	[17]
Li *et al.*	2023	Optical Glucometer	ML-based calibration	300	12 mg/dL	98%	[19]
He *et al.*	2024	Multi-signal	Transformer + LSTM	210	13 mg/dL	97%	[57]
Soliman *et al.*	2024	PPG	Hybrid CNN-GRU	190	14 mg/dL	96%	[86]

7. Clinical Performance Evaluation

7.1. Clarke Error Grid Analysis

Clarke Error Grid Analysis (CEGA) is a standard tool for assessing the clinical accuracy of glucose measurement systems by comparing predicted values with reference measurements and classifying them according to their potential impact on therapeutic decision-making [81, 82]. The grid is divided into five zones (A–E), where Zones A and B are considered clinically acceptable, while Zones C–E represent errors that may lead to inappropriate or potentially dangerous clinical interventions [55, 83].

The objective of CEGA extends beyond the evaluation of quantitative prediction errors; it emphasizes the clinical relevance of errors, thereby determining whether a measurement system is sufficiently reliable to support treatment decisions in real-world clinical settings [84].

7.2. Quantitative Performance Metrics

In addition to CEGA, the performance of glucose measurement models is commonly evaluated using statistical metrics such as accuracy, sensitivity, and specificity, which quantify the ability of the system to correctly identify normal and abnormal glycemic states [85].

For continuous regression tasks, error measures such as mean absolute error (MAE) and root mean square error (RMSE) are employed to reflect the average deviation between predicted and reference glucose values [47]. Furthermore, the coefficient of determination (R^2) indicates the proportion of variance in glucose levels explained by the model, with higher

values corresponding to better model fit and predictive capability [86].

In clinical practice, combining quantitative statistical metrics with Clarke Error Grid Analysis provides a more comprehensive assessment of accuracy, reliability, and clinical safety for non-invasive glucose monitoring systems [11].

8. Remaining Challenges

Although NIR–PPG demonstrates considerable potential for non-invasive glucose monitoring, its clinical deployment remains constrained by data-related and system-integration challenges. Universal calibration remains one of the most critical challenges in non-invasive glucose monitoring. Models trained on a specific cohort often exhibit significant performance degradation when applied to new individuals, primarily due to inter-subject variability in physiological and optical properties, including skin tissue composition, water content, melanin levels, and hemodynamic characteristics [10, 22, 38]. Although several approaches–such as signal normalization, transfer learning, and the removal of unwanted variance using techniques like orthogonal signal correction (OSC) and external parameter orthogonalization (EPO)–have been proposed, achieving a truly universal calibration model remains an open problem. Addressing this challenge requires large-scale, diverse datasets and the development of adaptive, generalizable modeling frameworks capable of maintaining robust performance across heterogeneous populations.

The lack of large-scale, multicenter datasets with standardized labeling limits the generalization capability of deep learning models [28], while data augmentation and transfer learning approaches have not yet been sufficiently validated under real-world clinical conditions [87].

Motion artifacts and inter-individual physiological variability distort PPG signals and induce instability in tissue optical properties, thereby reducing prediction reliability [22, 38]. In addition, environmental influences, the need for periodic calibration, and hardware-related issues–such as sensor drift, component aging, and inter-device variability–continue to hinder long-term stability and standardization [10,88,89].

Consequently, successful commercialization will require coordinated optimization across optical system design, adaptive signal processing, and self-calibrating machine learning models, integrated within a unified intelligent sensing architecture.

9. Conclusion

Near-infrared (NIR) spectroscopy is currently regarded as one of the most promising optical technologies for non-invasive glucose monitoring, owing to its ability to penetrate biological tissues and interact directly with chemical components associated with glucose. The integration of NIR spectroscopy with photoplethysmography (PPG), together with machine learning and deep learning algorithms, has significantly improved feature extraction, nonlinear relationship modeling, and overall prediction accuracy.

Nevertheless, despite substantial advances in signal processing, modeling techniques, and sensor design, existing NIR–PPG systems have not yet fully satisfied the stringent requirements necessary to replace invasive glucose measurement methods in routine clinical practice. Limitations related to physiological noise, personalized calibration, and long-term stability remain critical challenges that must be further investigated and addressed before this technology can be widely deployed for diabetes management.

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