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Assessment methodology for non-invasive glucose estimation based on biomedical signals targeting reproducible research

Metodologia de avaliação para estimativa não invasiva de glicose baseada em sinais biomédicos voltada à pesquisa reprodutível

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ABSTRACT

Objective: To propose a reproducible assessment methodology for artificial intelligence-based non-invasive glucose estimation using multimodal biomedical signals. **Method:** The workflow covers dataset composition, signal acquisition under non-ideal conditions, biomedical signal preprocessing, feature extraction, and machine learning model training and evaluation, with attention to small datasets, acquisition variability, and preprocessing degrees of freedom. A multimodal biomedical dataset and an executable signal-processing and artificial intelligence pipeline were made publicly available to support reproducible experimentation. **Results:** An execution of one reference configuration achieved a root mean squared error (RMSE) of 18.21 and a mean absolute error (MAE) of 15.28. However, performance was strongly limited by the small sample and should not be interpreted as evidence of generalization. The experiment neither identifies an optimal preprocessing configuration nor establishes the superiority of multimodal over single-modality representations. **Conclusion:** The proposed methodology supports more transparent and reproducible research in non-invasive glucose estimation.

Keywords: glucose; signal processing, computer-assisted; reproducibility.

RESUMO

Objetivo: Propor uma metodologia reprodutível de avaliação para a estimativa não invasiva de glicose baseada em inteligência artificial e sinais biomédicos multimodais. **Método:** O fluxo abrange composição da base de dados, aquisição em condições não ideais, pré-processamento de sinais, extração de características e treinamento e avaliação de modelos de aprendizado de máquina, com atenção às bases pequenas, à variabilidade de aquisição e aos graus de liberdade do pré-processamento. Uma base biomédica multimodal e um pipeline executável de processamento de sinais e inteligência artificial foram disponibilizados publicamente para apoiar experimentos reprodutíveis. **Resultados:** Uma execução de uma configuração de referência obteve raiz do erro quadrático médio (RMSE) de 18,21 e erro absoluto médio (MAE) de 15,28. Entretanto, o desempenho foi fortemente limitado pela pequena amostra e não deve ser interpretado como evidência de generalização. O experimento não identifica uma configuração ótima de pré-processamento nem demonstra superioridade da abordagem multimodal sobre modalidades isoladas. **Conclusão:** A metodologia contribui para pesquisas mais transparentes e reprodutíveis em estimativa não invasiva de glicose.

Descritores: glicose; processamento de sinais assistido por computador; reprodutibilidade.

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1 INTRODUCTION

This work investigates non-invasive glucose estimation using a multimodal dataset composed of photoplethysmography (PPG), electrocardiography (ECG), and bioimpedance signals, motivated by the need for improved diabetes monitoring. Diabetes Mellitus is a chronic disease characterized by impaired glucose regulation, leading to persistent hyperglycemia and long-term complications such as cardiovascular and renal diseases. Conventional glucose monitoring relies on invasive capillary blood collection using glucometers, lancets, and disposable test strips, which may be uncomfortable and inconvenient for continuous monitoring. Although Continuous Glucose Monitors reduce the need for repeated finger pricks, their high cost and lack of availability through the Brazilian Unified Healthcare System limit accessibility.

Recent advances in wearable health technologies, particularly smartwatches, have increased interest in non-invasive glucose estimation using PPG and companion physiological signals, particularly within the context of machine learning (ML). However, as discussed in the next section, recent studies present limitations regarding reproducibility, methodological transparency, and dataset availability. Limited evaluation methodologies may even introduce data leakage and artificially inflated performance metrics when ML is involved. Furthermore, although multimodal approaches combining PPG with other signals have recently emerged, there is currently no fully reproducible work integrating fingertip PPG, smartwatch ECG, and bioimpedance signals within a publicly accessible signal-processing and artificial intelligence (AI) pipeline for glucose estimation.

The main contribution of this work is an executable and configurable research framework for reproducible non-invasive glucose estimation, encompassing multimodal dataset organization, signal preprocessing, feature extraction, participant-wise validation, and machine learning model selection. The framework is supported by making the data used (PPG, ECG, bioimpedance, and capillary glucose measurements) publicly available. The work also presents a critical analysis of reproducibility in established PPG-based glucose estimation and classification studies, focusing on data leakage, demographic features, and the availability of datasets and source code. In addition, it discusses the challenges posed by small datasets and non-ideal acquisition conditions. The objective is not to identify a universally optimal pipeline configuration or establish clinical performance from the present pilot sample, but to provide an explicit and reproducible framework for future experimentation.

2 LITERATURE REVIEW OF REPRODUCIBLE PPG-BASED GLUCOSE ESTIMATION

The literature on non-invasive glucose estimation is vast, encompassing optical, electrical, and electromagnetic approaches, implemented through devices ranging from custom-built sensors to smartphones. The proposed solutions vary from signal-processing and AI algorithms applied to biomedical signals, to dedicated hardware specifically designed for glucose estimation. Among them, solutions based on the PPG signal have been widely studied due to the nature of the signal being relatively easy to obtain, based on illuminating a region of the human body that contains blood vessels with minimal tissue and fat layers, such as the finger or earlobe. The reflected portion of the light contains information about blood flow variation throughout the systolic and diastolic phases of the cardiac cycle.

Although PPG does not directly measure glucose concentration, glycemic changes, particularly hyperglycemia and diabetes-related physiology, are associated with changes in vascular function and arterial stiffness and microvascular or peripheral perfusion [1], which can modulate PPG waveform features and may therefore correlate with glucose in specific contexts. Features are extracted from PPG waveforms, including temporal, morphological, and frequency-domain, and are commonly combined with statistical or machine-learning models to estimate glucose levels. Prior studies report [2] that glucose levels can be estimated from this signal, particularly from the perspective of ML within the field of AI.

Since the PPG has an indirect relationship with glucose, it is particularly susceptible to physiological confounders such as heart rate variability, blood pressure, skin tone, and motion. As a result, PPG-based approaches have emphasized multimodal combinations of non-invasive signals and measurements, such as PPG with ECG and skin impedance, also called bioimpedance.

There is evidence that skin electrical impedance in conjunction with the PPG signal can be used to assess changes in skin resistance that may be related to variations in blood glucose levels [3]. In addition to electrical bioimpedance and the PPG signal, the ECG signal, which records the electrical activity of the heart and allows the evaluation of heart rhythm and detection of possible abnormalities, has been used to assess potential effects of glucose on its different segments [4]. It has also been used for blood glucose estimation [5], demonstrating that there is room for studies on non-invasive glucose monitoring based on this signal. A multimodal collection of data may result in a predictive model capable of estimating glucose levels non-invasively.

In this context, reproducibility is a fundamental requirement. The lack of reproducibility has contributed to what has been described as a "reproducibility crisis" in science [6]. In AI-based biomedical signal processing, reproducibility depends on factors such as methodological transparency, shared datasets and code, and detailed reporting of collection protocols and equipment [7]. A major challenge in biomedical AI is data leakage during model training and evaluation. Since physiological signals such as PPG and ECG are subject-dependent, datasets must be divided participant-wise to ensure that samples from the same individual do not appear simultaneously in training and testing sets. Similar leakage problems may occur when scaling or performing feature selection before dataset splitting.

Another important concern is the inclusion of demographic or subject-specific variables as model inputs. Features such as age, weight, sex, race, or subject identification numbers (IDs) may lead models to learn participant-specific characteristics rather than physiological patterns directly associated with the analyzed signals [8]. This is particularly relevant in glucose estimation, since factors like older age and heavier weight are associated with a higher risk of hyperglycemia and type 2 diabetes [9]. Consequently, the inclusion of these variables as model input may artificially improve predictive performance while reducing generalization capability. This work also analyzes reproducibility aspects in PPG-based glucose estimation and classification studies, including data and code availability, use of demographic features, and whether train and test sets were mutually exclusive between participants. Table 1 shows an analysis of reproducibility in works about PPG-based estimation or classification of glucose using AI techniques.

Early and highly cited work by Monte-Moreno [10] used data from 410 participants with subject-wise train/test splitting, but neither code nor dataset was made publicly available, and demographic variables such as age, weight, and body mass index were included as model features. Gupta et al. [11] proposed a custom PPG acquisition system using 26 participants and also incorporated body weight index as input, but intentionally mixed participant data between training and testing to create personalized models. Bent et al. [12] collected smartwatch and glucose-monitoring data, including food logs and demographics such as age, weight, glycated hemoglobin, and even the subject ID as a personalization marker, from 16 participants and made both data and code publicly available. They trained both a population model with leave-one-person-out validation and personalized temporal models.

Yang et al. [13] used fingertip infrared PPG signals from 290 participants and performed subject-wise train/test partitioning, although neither code nor data were released. Kermani and Esmaeili [14] employed Mel-frequency cepstral coefficients extracted from a publicly available dataset with 23 participants and included demographic variables such as age, sex, height, and weight; however, they used conventional 5-fold cross-validation without explicit subject-wise separation, and while data is available, code is not.

Zeynali et al. [15] trained deep learning models using the VitalDB dataset with 6,388 subjects and evaluated external generalization on the MUST dataset, but despite mentioning reproducibility and initially providing a repository link, the source code was later removed for "privacy and security reasons." Bui et al. [16] proposed a ring-based system using 47 participants. They added age and gender as input, with evidence suggesting subject-wise cross-validation despite the absence of explicit clarification. Finally, Ahuja, Malhotra, and Yadav [17] evaluated their method using patient-wise data splits and an independent held-out test set comprising data from 217 participants; however, neither the code nor the dataset was made publicly available.

Overall, the reviewed literature demonstrates growing interest in non-invasive glucose estimation using PPG and companion physiological signals. However, despite the promising results reported in recent studies, important limitations remain regarding reproducibility, methodological transparency, dataset availability, and robustness under realistic data acquisition conditions. Furthermore, although multimodal approaches combining PPG with signals such as ECG and bioimpedance have recently emerged as promising alternatives for improving robustness and physiological interpretability, reproducible end-to-end implementations remain scarce in the literature. To the best of the authors' knowledge, there is currently no fully reproducible work integrating PPG, ECG, and bioimpedance signals within a publicly accessible signal-processing and AI pipeline for glucose estimation. This observation is particularly relevant given that most of the referenced studies in Table 1 are recent, highlighting the timeliness of the methodology presented in the next section.

3 METHODS

This section presents the proposed end-to-end methodology adopted for non-invasive glucose estimation using multimodal biomedical signals, including PPG, ECG, and bioimpedance measurements. The section initially describes the dataset collected for this work, then important aspects of the signal processing and feature extraction pipelines are detailed, covering preprocessing and signal conditioning stages, fiducial point localization, quality-based segmentation, and the extraction of features.

Table 1. Reproducibility analysis on PPG-based glucose estimation and classification task

Study	Participants	Data available?	Code available?	Uses demographics?	Exclusive train/test?
Monte-Moreno (2011) [10]	410	No	No	Yes	Yes
Gupta *et al.* (2021) [11]	26	No	No	Yes	No
Bent *et al.* (2021) [12]	16	Yes	Yes	Yes	Yes
Yang *et al.* (2024) [13]	290	No	No	No	Yes
Kermani and Esmaeili (2025) [14]	23	Yes	No	Yes	No
Zeynali *et al.* (2025) [15]	6,388	Yes	No	No	No
Bui *et al.* (2025) [16]	47	No	No	No	Yes
Ahuja *et al.* (2026) [17]	217	No	No	No	Yes

Source: Prepared by the authors (2026).

3.1 Collected dataset and data collection protocol

Data was collected to investigate associations between capillary glucose levels and non-invasive physiological signals, including PPG, ECG, and bioimpedance. The resulting IEB-3 dataset comprises eight volunteers from the Institute of Biomedical Engineering of the Federal University of Santa Catarina (IEB-UFSC) assessed during routine daily activities, without fasting requirements or venous blood collection. Capillary glucose was measured using a glucometer. All participants provided written informed consent, and the study was approved by the Human Research Ethics Committee at UFSC under CAAE 84846024.9.0000.0121.

Blood pressure was measured using an Omron HEM-7122 monitor, ECG was recorded for 30 seconds using a Samsung Galaxy Watch6 smartwatch twice, and PPG signals were collected for three minutes using a transmission-type pulse oximeter connected to a custom IEB-UFSC acquisition system operating at a sampling rate of 500 Hz [18]. Bioimpedance measurements were performed on the inner forearm using four ECG electrodes and the 4E-IA four-electrode impedance analyzer developed by Torsvik [19] at the University of Oslo, in a frequency sweep setting ranging from 10 Hz to 2 MHz. The setup used an Analog Discovery 3 for waveform generation and acquisition.

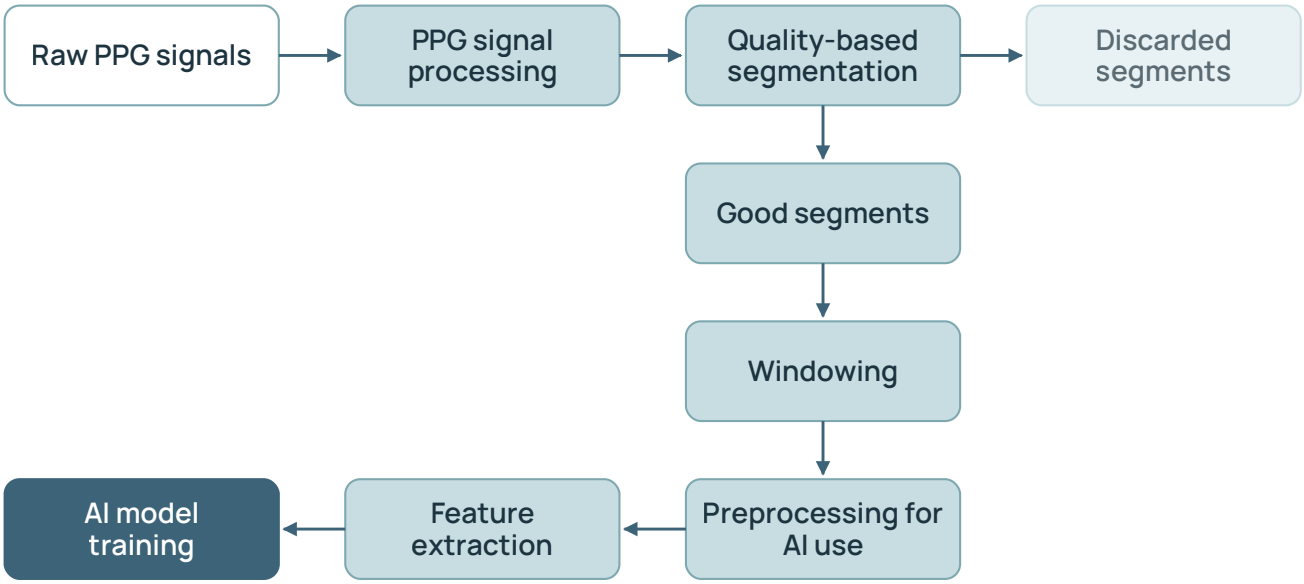
Glucose was measured by the researcher using capillary blood obtained by finger prick and a G-Tech Free glucometer with sterile disposable lancets. Each acquisition session was defined by one capillary glucose measurement and the corresponding PPG, ECG, bioimpedance, and blood pressure acquisitions performed during the same collection visit. The modalities were associated at the participant-session level and were not treated as independent glucose observations. As with the PPG and ECG acquisitions, the bioimpedance measurement procedure was non-invasive, and the current level was well below the threshold of human perception. A summary of the glucose profile per participant can be seen in Table 2. The current IEB-3 dataset comprises eight participants and 29 acquisition sessions, with limited glycemic variability. It was used to demonstrate the proposed data collection and processing workflow, which can support the incorporation of additional participants and sessions if the dataset is expanded.

Table 2. Participant-level glucose profile of the IEB-3 dataset

Participant	Number of sessions	Mean Glucose (mg/dL)	Min Glucose (mg/dL)	Max Glucose (mg/dL)
ieb_01	6	112	94	125
ieb_02	10	106.4	92	124
ieb_03	3	98	83	116
ieb_04	4	114.5	97	141
ieb_05	1	84	84	84
ieb_06	1	94	94	94
ieb_07	2	93.5	93	94
ieb_08	2	126.5	88	165

Source: Prepared by the authors (2026).

Figure 1. Block diagram of the PPG signal processing and feature extraction stages in the proposed methodology. Similar stages were adopted for the ECG and bioimpedance signals



Source: Prepared by the authors (2026).

Signal processing

The proposed pipeline separates preprocessing, quality assessment, segmentation, windowing, feature extraction, and model evaluation, as illustrated in Figure 1. These stages contain configurable degrees of freedom that may affect performance, particularly in small datasets collected under non-ideal conditions. The reported parameters define an executable reference configuration rather than universally optimal values, and alternative configurations can be evaluated through the publicly available implementation. Filtering was used to attenuate baseline wander, motion artifacts, and high-frequency noise while preserving physiologically relevant waveform characteristics. High-quality intervals were subsequently divided into analysis windows, from which temporal, morphological, spectral, and variability-related features were extracted and organized into structured multimodal datasets.

3.2 Segmenting according to a quality indicator

Signal quality was assessed independently for each modality. PPG and ECG used NeuroKit2 template-matching signal quality indices (SQIs), while bioimpedance quality was estimated from the consistency between the normalized curve and a smoothed reference. SQI values were normalized to the range [0,1], and continuous intervals exceeding modality-specific thresholds were retained for windowing and feature extraction. When multiple valid intervals were available, the highest-quality interval was prioritized.

3.3 Preprocessing for AI use: PPG and ECG fiducial point detection

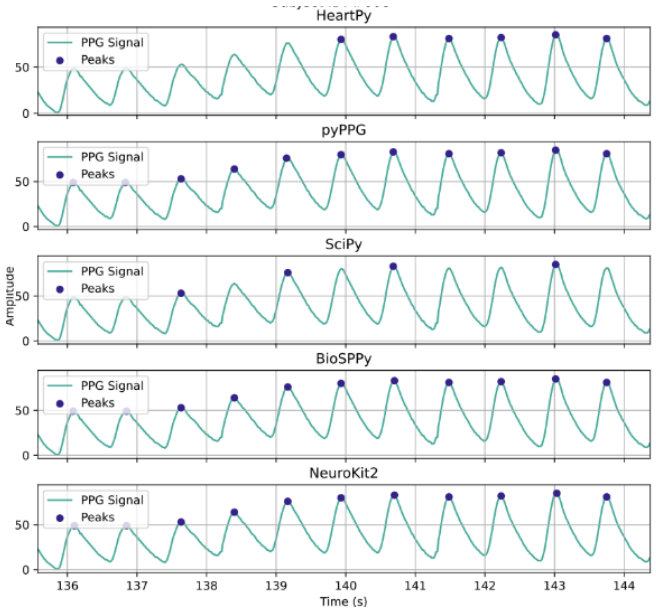
PPG morphological features and ECG-derived descriptors depend on accurate fiducial localization, particularly pulse onsets, systolic peaks, pulse intervals, and ECG R-peaks. Detection errors may propagate to downstream features, making the choice of fiducial detection method an important processing degree of freedom. Generic local-maximum detection, such as SciPy's *find_peaks* implementation [20], may be sensitive to motion artifacts and amplitude variations. Figure 2 compares implementations from HeartPy [21], pyPPG [22], SciPy, BioSPPy [23], and NeuroKit2 [24]. In the recordings examined during pipeline development, NeuroKit2 provided more consistent peak localization and was therefore adopted for PPG and ECG fiducial detection in this project.

3.4 Feature extraction

Features were extracted independently from PPG, ECG, and bioimpedance using modality-specific processing pipelines. PPG signals were filtered using a zero-phase fourth-order Butterworth band-pass filter from 0.5 to 4.0 Hz at a sampling rate of 500 Hz. Signal quality was assessed using the NeuroKit2 template-matching SQI. In the reference configuration, SQI thresholds were set to 0.95 for PPG and 0.5 for ECG, with a minimum valid segment duration of 10 s. Valid segments were divided into 5 s windows with a 2 s shift. Extracted PPG features included heart-rate and SQI statistics, beat-level morphological descriptors, Welch power spectral density features, and PPG-derived time-domain heart rate variability (HRV) measures. Given the short recording durations, ECG and PPG-derived HRV

calculations were included only as exploratory descriptors. The features remain configurable in the available implementation.

Figure 2. Comparison of estimated systolic peaks in a raw PPG segment among different biomedical signal processing libraries



Source: Prepared by the authors (2026).

ECG processing used NeuroKit2 for signal cleaning, R-peak detection, and instantaneous heart-rate estimation. Extracted features included heart-rate statistics, HRV descriptors, RR-interval statistics, and a signal-quality proxy defined as the proportion of estimated heart-rate values within the physiological range of 40–180 bpm. Each bioimpedance curve was summarized using a low-dimensional set of descriptors comprising mean, standard deviation, mean gradient, gradient standard deviation, and peak-to-peak amplitude.

Feature vectors were aligned using participant and acquisition-session identifiers. When modalities produced different numbers of vectors within the same session, vectors from the modality with fewer observations were repeated to match the largest set. Repeated rows retained their original participant and session identifiers, and participant-grouped partitioning kept all rows from the same participant within a single training, validation, or test partition. This prevents repeated representations from crossing participant-level partitions but does not make them independent and may alter the relative weighting of sessions. The dataset therefore comprises 29 acquisition sessions nested within eight participants, regardless of the number of generated multimodal rows. Session-level aggregation remains an alternative alignment strategy for future work.

4 RESULTS

4.1 Developed software

The developed software framework was written in Python and designed to support reproducible machine learning experiments involving biomedical waveforms such as PPG, ECG, and bioimpedance. The framework combines the use of Pandas DataFrames for structured metadata handling and the SigMF standard for efficient storage of waveform signals and associated metadata. This approach enables organized management of sampled biomedical signals, annotations, segments, events, and machine learning features while facilitating reproducibility across different pipelines.

A central design objective of the framework is the effort to prevent methodological inconsistencies and data leakage in biomedical artificial intelligence experiments. To address these matters, the framework organizes datasets around unique waveform identifiers and maintains explicit relationships between raw signals, generated waveforms, extracted segments, detected events, and derived machine learning features. This organization facilitates participant-wise dataset partitioning, via, for example, group cross-validation, and traceability throughout the complete signal processing pipeline. The link to the code and data is available in the Data and materials availability statement. To ensure privacy, all sensitive data pertaining to the volunteers was anonymized, with direct participant identifiers being study-specific codes. The shared dataset contains only the variables required to reproduce the reported analyses.

4.2 Machine learning results

The motivation in this subsection is not to present final numbers with respect to accuracy, but to illustrate the diverse results that can be obtained with the flexibility enabled by the proposed methodology. When concatenating the features of all modalities (PPG, ECG, and bioimpedance), the total number of features is 121. Not all features are useful and the number can be reduced via automatic feature selection algorithms.

Feature relevance and stability were examined separately using Recursive Feature Elimination (RFE) within a Leave-One-Subject-Out (LOSO) framework. In each iteration, normalization and RFE were fitted exclusively using the training participants with a predefined RFE-compatible estimator. Feature stability was quantified by selection frequency across the eight folds. Among the 20 most frequently selected features, 19 were derived from PPG, one from bioimpedance, and none from ECG. This analysis was conducted independently from the subsequent regression model comparison.

Table 3. Nested participant-grouped cross-validation results for the reference configuration

Model	Mean RMSE	RMSE Std	Mean MAE	MAE Std
Gradient Boosting Regressor	18.21	15.45	15.28	13.44
Random Forest	19.41	13.55	17.51	11.66
Support Vector Regressor	26.28	14.88	22.97	12.67
Gaussian Process Regressor	29.17	14.23	26.86	12.93
K-Nearest Neighbors	33.21	21.65	30.38	19.59
Ridge Regression	39.66	20.11	37.48	19.19
Elastic Net Regression	48.63	20.56	45.61	20.31
Lasso Regression	49.87	25.98	47.23	22.97

Source: Prepared by the authors (2026).

Regression models were compared using the original multimodal feature representation and nested participant-grouped cross-validation. Participants were assigned to mutually exclusive training, validation, and test partitions, and the training and validation partitions were combined into a development set. Within this development set, five outer GroupKFold splits were used for performance estimation, while three inner GroupKFold splits were used for hyperparameter selection through GridSearchCV. RFE was not applied during this stage. Eight regressors were evaluated: Ridge, Lasso, ElasticNet, support vector regression, Gaussian process regression, k-nearest neighbors, Random Forest, and gradient boosting. Standardization was included in the pipelines of the non-tree-based models.

Table 3 presents the aggregated results obtained across the five outer participant-grouped cross-validation folds. These results should be interpreted descriptively, as an illustration of performance variability across regression models within the proposed reproducible pipeline, rather than as evidence of high predictive accuracy or statistically established model superiority. The models with the numerically lowest mean root mean squared error (RMSE) values were gradient boosting and Random Forest, with mean RMSE values of 18.21 and 19.41, respectively. Nevertheless, the large standard deviations across folds indicate substantial uncertainty regarding their generalization capability.

In this context, methodological rigor becomes more important than reporting isolated mean absolute error (MAE) or RMSE values. Factors such as strict participant-wise separation, avoidance of data leakage, fitting preprocessing operations exclusively on training data, and grouped hyperparameter selection are fundamental for reliable evaluation. Moreover, the large standard deviations observed across folds reinforce the difficulty of the task and the influence of participant variability. Therefore, the numerical differences among regressors should not be interpreted as evidence of definitive model superiority.

5 CONCLUSIONS

This work presented a reproducible methodology for non-invasive glucose estimation based on multimodal biomedical signals, covering data acquisition, dataset organization, signal processing, feature extraction, feature selection, and machine learning evaluation. The framework emphasizes methodological transparency, participant-wise validation, prevention of data leakage, and explicit documentation of processing and modeling decisions. The reference execution showed substantial variability across validation folds, reinforcing the need for cautious interpretation of performance metrics. The study demonstrated the feasibility of integrating PPG, ECG, and bioimpedance within a common and executable framework, but did not establish that multimodal representations outperform individual modalities. The publicly available implementation supports reproduction of the reported configuration and evaluation of alternative decisions. Larger and more diverse datasets are required to assess parameter sensitivity, modality-specific contributions, and external generalization.

Author contributions. S.P.K. was responsible for data collection, data processing and analysis, interpretation of results, and preparation of the original manuscript. C.R.R. contributed through scientific supervision, methodological guidance, and critical review and revision of the manuscript. Both authors contributed to the development of the study and approved the final version of the manuscript.

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Data and materials availability. The source code and dataset used are available at: https://github.com/sklautau/multi-sig-glc/.

Conflicts of interest. The authors did not declare any conflicts of interest.

Use of artificial intelligence. ChatGPT was used for text revision, and GitHub Copilot was used for support in writing AI code and debugging. All generated suggestions were reviewed and validated by the authors.

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EDITORIAL NOTES

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