Continuous Blood Glucose Monitoring using Machine learning techniques

A Synopsis submitted to Gujarat Technological University

For the Award of

Doctor of Philosophy

In

Electronics and Communication Engineering

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[January -2026]

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1 Title of the thesis and abstract

1.1 Title of the thesis

Continuous Blood Glucose monitoring using machine learning techniques

1.2 Abstract

Over 500 million people worldwide currently have diabetes, a number projected to reach 783 million by 2045. Effective blood glucose monitoring is crucial, especially for those with Type 1 diabetes (T1D), who require exogenous insulin for management. Continuous blood glucose monitoring (CGM) aids in tracking glucose levels but relies on invasive blood sampling, which can be painful and pose infection risks. Current CGM systems calculate insulin bolus doses based solely on current blood glucose levels, failing to account for the variability in carbohydrate intake at meals. This often leads T1D patients to experience hypoglycaemic and hyperglycaemic episodes. If not managed properly, high blood glucose can result in serious complications, such as cardiovascular disease, neuropathy, nephropathy, and eye disease. Overall, achieving effective glycaemic control in diabetes management remains a significant challenge. To tackle these challenges, this research aims to create a non-invasive continuous glucose monitoring (CGM) system that includes machine learning-based blood glucose (BG) measurement, BG forecasting, and insulin bolus calculation based on predicted future BG readings to enhance glycaemic control.

The proposed CGM system uses a non-invasive, single-sensor device at 940 nm to acquire physiological signals and generate a structured dataset. The Shapley additive explanation method is applied to the dataset to identify important features for blood glucose estimation. A lightweight machine learning based distributed architecture continuously estimates blood glucose (BG) levels, and a forecasting model predicts future BG for a 60-minute horizon. This forecast, along with carbohydrate intake and individual characteristics, is used to calculate bolus insulin dosages. The impact of intermittent insulin boluses is tested using 10 in-silico adult cohorts from the UVA/Padova T1D simulator across various meal and insulin scenarios.

The evaluation shows that the proposed continuous glucose monitoring (CGM) system provides accurate blood glucose (BG) readings, with a root mean square error (RMSE) of 6.08 mg/dL and a mean absolute difference (MAD) of 1.79 mg/dL. The proposed hybrid architecture for forecasting demonstrates improved performance, achieving root mean square errors (RMSEs) of 3.42, 6.45, and 17.73 mg/dL for virtual subjects, and 12.57, 20.72, and 34.41 mg/dL for real subjects at prediction horizons (PH) of 15, 30, and 60 minutes, respectively. Additionally, the mean absolute error (MAE) for 15-, 30-, and 60-minute prediction horizons is 2.11, 4.47, and 11.78

mg/dL for simulated subjects, and 7.9, 14.13, and 25.5 mg/dL for real subjects. It improves glycaemic stability, with 98.86% of time spent in the target range (70-180 mg/dL), and reduces the risk of hyperglycaemia and hypoglycaemia, as indicated by mean values of the high BG index (HBGI) at 0.46, low BG index (LBGI) at 1.27, and blood glucose risk index (BGRI) at 7.49. Control-Variability Grid Analysis (CVGA) confirms the clinical applicability, showing that all virtual patients' BG levels are within zones A and B.

The proposed machine learning-based continuous glucose monitoring system offers a convenient and non-invasive solution for managing Type 1 Diabetes (T1D). This system enhances glycaemic control by using forecasting to make insulin dosing decisions. It holds significant potential for future use in intelligent, personalized diabetes care systems.

2 Brief description on the state of the art of the research topic

Continuous Glucose Monitoring (CGM) aids in the management of diabetes by providing real-time information on blood glucose (BG) levels throughout the day and night [1]. It is especially beneficial for individuals with diabetes who rely on multiple daily insulin injections or insulin pumps, such as those with Type 1 diabetes (T1D). It can also be helpful for some people with Type 2 diabetes. BG levels can be measured through either invasive or non-invasive methods. The invasive method involves obtaining blood by puncturing the fingertip to measure BG levels. The need to take multiple BG readings every day can make the process of using CGM uncomfortable and inconvenient. Non-invasive CGM sensors, which detect glucose molecules in the blood without the need to puncture the fingertips, offer a more practical solution for monitoring glucose levels.

Several non-invasive methods for estimating BG levels have been reported in the literature. Optical biosensors [2] and electrochemical glucose sensors [3] utilize saliva for glucose estimation. Additionally, Impedance spectroscopy [4] and Terahertz time-domain spectroscopy [5] can assess BG levels from the skin. However, saliva and skin exhibit different electrical characteristics that can vary from person to person. As a result, these methods may not provide precise BG measurements. Another approach studied is photo-acoustic spectroscopy-based BG estimation [6], which employs two pulsed laser diodes and requires a complex setup. Currently, a near-infrared (NIR) based method that utilizes short NIR wavelengths is also gaining popularity [7]. The process of NIR based BG estimation is illustrated in Fig. 1, which provides a conceptual diagram for better understanding. This method involves passing a specific wavelength of infrared light through the blood. Glucose in the blood absorbs these rays, which are then measured on the other side. By comparing the emitted and captured rays, the BG level is indirectly determined as an analog

electrical signal equivalent to the glucose level in the blood. The microcontroller's analog-to-digital converter (ADC) is used to transform this signal into digital data. This data is utilized to train a Machine Learning (ML) model to estimate BG level. A non-invasive BG measurement device has been developed that uses three infrared (IR) sensors, each operating at different wavelengths, to assess BG levels [8]. Additionally, physiological parameters are incorporated into the measurement process alongside these sensors [9].

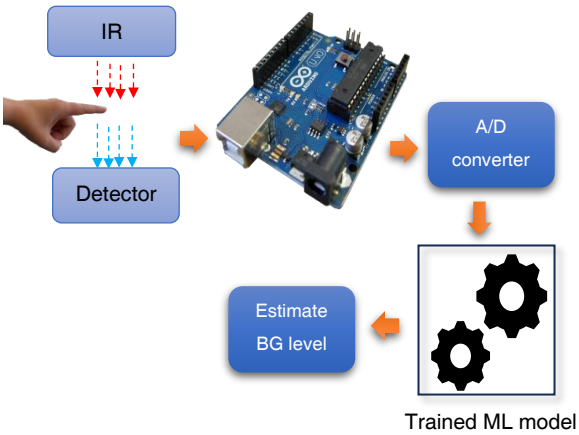

Fig. 1 Conceptual diagram for BG estimation process using NIR spectroscopy

In continuous glucose monitoring (CGM) systems, forecasting blood glucose levels is essential for managing post-meal blood sugar control. By predicting fluctuations in advance, it allows for immediate and proactive corrective actions. Recent research emphasizes the use of artificial neural networks (ANNs) and other machine learning (ML) techniques for their effectiveness in predicting future blood glucose levels, optimizing insulin delivery, and identifying hypoglycaemic and hyperglycaemic episodes early [10]. Inaccurate or delayed glucose forecasts can lead to incorrect insulin dosages, increasing the risk of hypoglycaemic and hyperglycaemic episodes, which may result in hospitalization or permanent organ damage. Recent studies have employed recurrent and convolutional neural network architectures to create clinically useful BG forecasting models. Compared to traditional methods, these models have shown improved performance on clinically relevant error metrics and have reduced root mean square error (RMSE) [11], [12], [13]. Recent efforts have concentrated on personalized strategies, such as hybrid multimodal networks that utilize attention-based deep learning frameworks. These networks integrate data from glucose levels, insulin, meals, and physical activity. Additionally, there are incrementally retrained LSTM models that adapt to each patient's CGM history [14]. Predicting BG levels accurately remains challenging due to multiple factors that affect glucose levels beyond just insulin infusions. Previous research has explored how these factors can be used as input components in BG forecasting, which has led to improved accuracy across various prediction horizons (PHs) [15]. Incorporating features like food intake, insulin dosage, and step count, Kalman-smoothed stacked

LSTM models for Type 1 Diabetes (T1D) patients show significantly low RMSEs at 30- and 60-minute time frames. However, due to the smoothing effects, these models generally struggle with accuracy during extreme glucose levels and rapid fluctuations in glucose [16]. Hybrid architectures that combine convolutional feature extractors with sequence models have consistently demonstrated superior accuracy in short- and mid-term glucose forecasting [17]. The Convolutional Recurrent Neural Network (CRNN) enhances short-term glucose prediction accuracy; however, its ability to model very long-term dependencies is limited, and its high computational cost affects overall performance [18]. Although the hybrid CNN-GRU model outperforms single-model baselines in real-time blood glucose forecasting, its generalizability is constrained by its reliance on a single-patient dataset, the lack of validation across diverse populations, and shorter prediction timeframes [19].

Daily injections of long-acting insulin, continuous subcutaneous insulin infusion, or insulin pump therapy are standard treatments for type 1 diabetes (T1D). These methods help reduce postprandial glucose spikes and keep blood glucose levels within the target range of 70–180 mg/dL [20]. The use of insulin pumps has recently increased due to advancements in closed-loop (CL) and artificial pancreas (AP) insulin technologies [21]. An intermittent closed-loop approach designed for individuals using multiple daily injections (MDI) has been presented in recent modelling work, which demonstrated in silico that partial automation could improve glucose management without transitioning to pump therapy [22]. In a prospective observational study, regular monitoring and continuous follow-up improved the glycaemic outcomes of T1D patients on MDI [23]. Recent advancements in insulin pump technologies, like closed-loop systems and tubeless options, show promise for improving clinical practices. However, challenges such as technical complexity, high costs, limited accessibility, constant sensor connectivity needs, and frequent calibration hinder widespread adoption. As a result, many individuals with Type 1 Diabetes (T1D) still rely on MDI therapy for their insulin needs [24]. In MDI therapy, rapid-acting insulin manages postprandial hyperglycaemia, while long-acting insulin meets basal needs. Doctors regularly adjust doses based on patient characteristics. A key advantage of MDI over automated systems like AP is that T1D patients avoid wearing external devices or permanently using insulin pumps. The review highlights new insulin delivery methods that may improve kinetics and reduce injection burden, but lacks direct clinical trials to prove any innovative system outperforms optimized MDI therapy [25]. Research has shown that open-loop Multiple Daily Injection (MDI) therapy, when combined with Continuous Glucose Monitoring (CGM), consideration of individual characteristics, and optimal dosage calculations, can provide significant benefits for glycaemic control and remains a practical option [26]. Notably, MDI is an accessible choice for individuals with T1D, as optimizing bolus

therapy is a necessary alternative to Automated Insulin Delivery (AID) systems or insulin pump therapies. This approach is vital for improving patient outcomes for those who prefer injection-based treatments [27]. The standard formula-based open-loop MDI therapy takes into account individual characteristics. However, the dosages calculated using this formula may not offer sufficient glycaemic control [28]. These identified limitations underscore the ongoing need for improved MDI therapy methods alongside CGM. The goal of these advancements is to achieve similar levels of glycaemic stability and safety through predictive, data-driven insulin dosing strategies, while avoiding reliance on fully automated systems.

3 Definition of the Problem

Despite significant advances in diabetes technology, there remains a shortage of reliable, comfortable, and intelligent continuous glucose monitoring (CGM) systems that can operate non-invasively while also facilitating proactive glucose control. CGM systems predominantly rely on invasive methods for estimating glucose levels and calculating insulin doses based on current glucose readings. This approach offers limited support for predicting future glucose changes, resulting in insulin dosing decisions that are often reactive. Consequently, this leads to delayed interventions, increased glucose variability, and a heightened risk of hypo- and hyperglycaemic events. These limitations underscore the need for an integrated CGM framework that includes non-invasive, accurate glucose estimation, short-term glucose forecasting, and optimal insulin dosage calculation to enable timely and effective management of glycaemic levels.

4 Objective and Scope of work

4.1 Objectives

Effective management of diabetes mellitus necessitates precise and continuous blood glucose monitoring (CGM) to reduce the risks of severe hyperglycaemia and hypoglycaemia in individuals with Type 1 Diabetes (T1D). However, existing CGMs often rely on invasive techniques and static insulin bolus calculations, which can limit their effectiveness, leading to decreased patient compliance and therapeutic efficacy. This research aims to identify important features for BG estimation and develop a non-invasive, computationally efficient framework for accurately measuring and forecasting BG levels in real time. Building on this predictive capability, the study seeks to achieve the following specific goals:

- Develop algorithms to calculate the optimal bolus insulin dose for each meal.

- ❖ Design a robust intermittent bolus insulin therapy that utilizes predictive modelling to significantly enhance overall glycaemic stability and minimize variability throughout the day.

4.2 Scope of work

This research focuses on implementing a new machine learning-based system for CGM and control that non-invasively estimates BG levels. The study involves creating a structured dataset using a single-sensor, non-invasive device that uses 940 nm wavelength. The research also focuses on identifying important features for BG estimation. Additionally, it includes the design of a computationally efficient, lightweight, and distributed machine learning model for continuous blood glucose estimation.

The project also involves creating a short-term BG forecasting model that predicts glucose levels for up to 60 minutes in advance. This model will help anticipate future glucose trends. Based on these forecasted glucose values, a framework for calculating predictive insulin bolus doses is implemented to enhance glucose control during meals with intermittent insulin therapy. Finally, the proposed approach is evaluated using various metrics to assess how effectively it improves glycaemic control and reduces glucose fluctuations. The study excludes fully automated closed-loop insulin delivery devices and is limited to intermittent insulin therapy.

5 Original contribution by the thesis

- ❖ In this thesis, a non-invasive CGM system is proposed that includes machine learning-based BG measurement, BG forecasting, and intermittent insulin bolus calculation to enhance glycaemic control against daily carbohydrate variation across meals.
- ❖ This thesis proposes a simpler, non-invasive single-sensor device for continuously measuring BG levels. To evaluate the effectiveness of this continuous BG measurement device, a new database containing data from 784 individuals has been created for this research. Additionally, Shapley additive explanations are used to identify 13 important features from the collected data to improve BG estimation performance
- ❖ This thesis presents a lightweight two-level distributed architecture that utilizes a random forest model to measure BG levels with improved accuracy. The proposed architecture demonstrates superior performance in estimating BG levels, achieving a RMSE of 6.08 mg/dL, a mean absolute deviation (MAD) of 1.79 mg/dL, and a mean absolute relative deviation (mARD) of 1.5%. Additionally, Clarke Error Grid (CEG) analysis confirms the effectiveness of this architecture.

- In this thesis, a compact hybrid architecture, DCRNet, is proposed for BG forecasting that combines a dilated convolutional layer with an LSTM network. The dilated convolutional neural network (DCNN) benefits from a broader receptive field, which enhances its ability to process long, multidimensional signals. At the same time, the LSTM effectively captures nonlinear stochastic relationships among multiple inputs. An in-silico dataset is created to test the efficacy of a hybrid forecasting architecture that uses time-series BG data points and carbohydrate intake from 1,344 meal scenarios across 11 in-silico adult subjects with T1D, generated using the UVA/Padova T1DM simulator.
- In this thesis, a proposed intermittent insulin bolus (IIB) therapy utilizes forecasted glucose levels generated by a predictive model, replacing the conventional practice of using current blood glucose values to calculate bolus insulin doses.
- The proposed IIB therapy outperforms the conventional MDI and artificial pancreas system, achieving 99% time in the targeted range (TIR%) of 70-180 mg/dL across 10 virtual adult cohorts. This therapy also decreases the incidence of hyper- and hypoglycaemia and improved overall glycaemic control. The proposed therapy is safe and improves the quality of BG control, as the BG levels of all virtual patients lie in Zones A and B on the Control-variability grid analysis (CVGA).
- The proposed CGM system offers optimal glycaemic control with just three insulin doses per day. This approach gives patients more freedom from being tethered to external devices or relying on an insulin pump, compared to traditional automated insulin delivery systems (artificial pancreas).

6 Methodology of Research, Results / Comparisons

The proposed CGM system consists of four key components: non-invasive CGM data generation, BG measurement, BG forecasting, and intermittent insulin bolus (IIB) therapy. Fig. 2 illustrates the details of the proposed CGM system. In the non-invasive CGM data generation phase, subjects place their fingers into a non-invasive CGM sensor-based device that continuously captures BG levels. A dataset is created from the CGM data of real subjects, along with other relevant information about them. During data preprocessing, this dataset is cleaned to remove outliers, fill in missing data, perform data augmentation, and normalize the data. Key features are finalized using this refined dataset, which are then used for accurate BG level measurement.

This processed and normalized data is fed into a machine learning (ML) model, which estimates the current BG level (G). Next, in the BG forecasting phase, a hybrid deep learning (DL) model utilizes the most recent six BG samples, along with information on carbohydrate intake (C) and

current active insulin (I), to forecast BG levels one hour in advance. This advance forecasting enables better planning for future glucose management strategies.

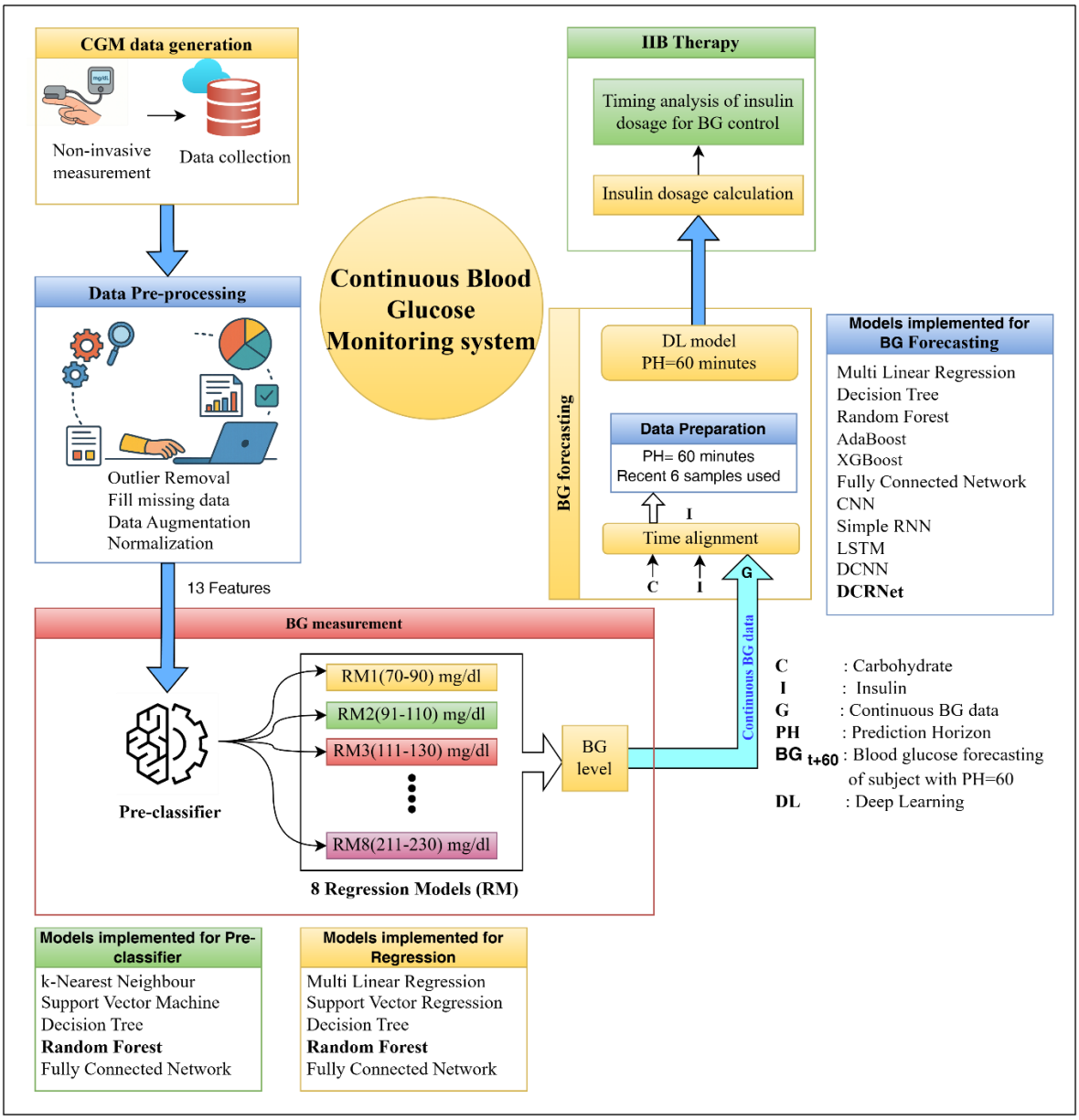

Fig. 2 Proposed continuous blood glucose monitoring system

In terms of IIB therapy, the forecasted BG level (denoted as BG_{t+60}) is used by a standard insulin dosage calculation formula to determine the meal-time insulin bolus (MIB). This formula helps establish the appropriate amount of insulin to take with each meal, rather than relying solely on current BG readings. Once the optimal bolus amount is calculated, the next step is to identify the timing for insulin administration at each meal. This timing is crucial for effectively managing postprandial BG levels and ensuring optimal glycaemic control throughout the day. Overall, this therapy enhances diabetes management effectiveness and improves glycaemic control, helping individuals feel more confident in managing their BG levels throughout the day.

6.1 Dataset generation

A non-invasive device integrated with a 940 nm single infrared sensor was kept at the Shreenath Clinical Laboratory, Valsad, Gujarat, India, for four months, from August to November 2023, for data collection. During this study, a total of 784 people's BG data and other relevant details like gender, age, height, weight, systolic blood pressure, diastolic blood pressure, duration of diabetes, heart rate, diabetes history, sleep time, slip quality, smoking, alcohol habit, walking, and serum BG were collected in the laboratory.

6.1.1 Data preprocessing

The non-invasive device measures multiple continuous readings that indirectly estimate the BG levels in the human body. Readings that fall outside a specific range are considered outliers. The inter-quartile range (IQR) approach is used to locate readings of this type. The average of all remaining readings is considered an analogous BG level for the individual after the outlier is removed. After removing outliers, a total of 552 people's BG data is used for further processing. Missing values are filled using the averaging method.

6.1.2 Feature importance

After refining the dataset, the Shapley Additive Explanation (SHAP) method is applied to identify the features that significantly contribute to blood glucose (BG) estimation. SHAP calculates the shapley values for each feature of complex model to find out the contribution of features in predicting output. Shapley value is defined in Eq. 1. This process allows us to eliminate the least important features, thereby simplifying the ML model.

$$\emptyset_j(x) = \sum_{s \subseteq \{x_1, x_2, \ldots, x_m\} \setminus \{x_j,\}} \frac{|s|!(m-|s|-1)!}{m!} (val\ (s \cup \{x_j\} - val(s))) \quad (1)$$

Where, $\emptyset_j(x)$ presents Shapley value of x_j, x_j is a value of feature, s is a subgroup of the model for a given feature, m represents the number of features available and val is the corresponding predicted feature values.

As illustrated in Fig. 3, smoking and alcohol features are dropped and finalized 13 important features after using SHAP. These features, which are used to train the BG estimation model, include gender, age, height, weight, systolic blood pressure, diastolic blood pressure, duration of diabetes, heart rate, diabetes history, sleep duration, sleep quality, physical activity (walking), and device readings. The serum BG collected from laboratory tests serves as the target value.

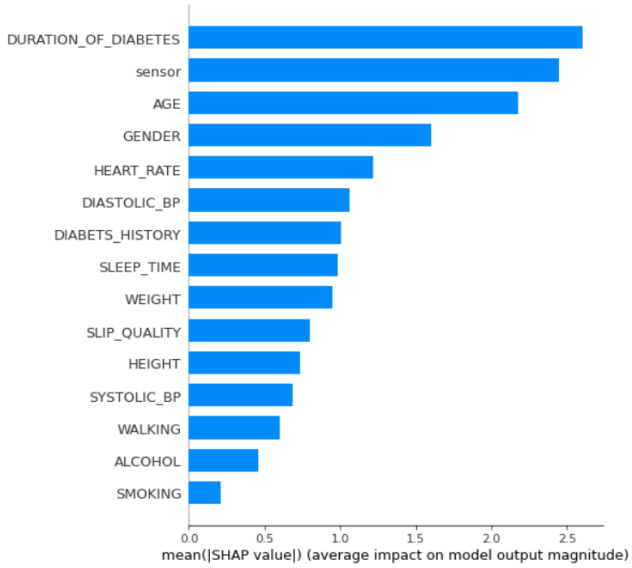

Fig. 3 Feature importance using Kernel SHAP

6.1.3 Data augmentation

The dataset collected for this study was limited in both the number of records and the variety of data, which may have resulted in underfitting and restricted the model's overall performance. Data augmentation is an effective method for addressing these issues and enhancing the model's performance. In light of this, data augmentation is applied to the collected records, increasing the dataset size to 17,898 entries.

6.1.4 Normalization

All data points are normalized to the range [0, 1] using the Min-Max scaler (Eq. 2) to train the model effectively. The dataset is split into 80% for training and 20% for testing.

$$Min\_Max\ X' = \frac{X - X_{min}}{X_{max} - X_{min}} \tag{2}$$

6.2 Proposed Lightweight Distributed Architecture for BG measurement

When machine learning models are trained on an augmented dataset, their performance often falls short. Upon investigating these issues in detail, we identified specific characteristics that vary by group. The model performs better when trained with a specific range of BG data. Therefore, instead of using a single architecture, a Distributed Architecture is proposed that includes a pre-classifier and several regression models. As illustrated in Fig. 4, this distributed architecture divides the training dataset into eight subsets. The first subset contains data from individuals with BG levels between 70-90 mg/dL, the second from 91-110 mg/dL, and so on. These subsets represent an eight-class set used to train the pre-classifier. Additionally, eight regression models are separately trained using these subsets, with each model focused on just one subset. During testing, the dataset is

processed through the pre-trained pre-classifier, and the classified outputs are then directed to their respective regression models.

6.2.1 Performance evaluation and result analysis of Distributed Architecture

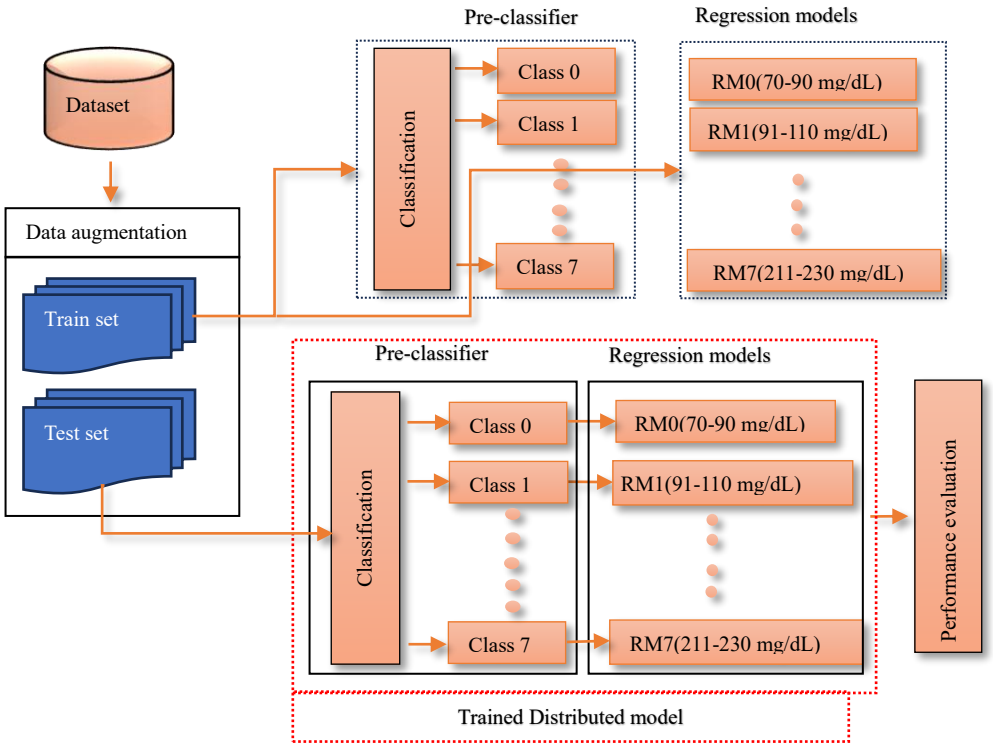

Fig. 4 Proposed Distributed architecture for BG estimation

In this research, we implemented several pre-classifiers: K-Nearest Neighbours (KNN), Support Vector Machine, Decision Tree, Fully Connected Network, and Random Forest. We then compared their performance to identify the most suitable architecture. Table 1 presents the evaluation results for the pre-classifiers. Accuracy, precision, recall, and F1 score are metrics used to evaluate the performance of classification models. Table 2 summarizes the results of the regression models. Multiple Linear Regression (MLR), Support Vector Regression (SVR), Decision Trees (DT), and Random Forest (RF) were applied for the regression tasks following the pre-classification stage. Root Mean Square Error (RMSE), Mean Absolute Relative Difference (mARD), and Mean Absolute Deviation (MAD) are all metrics used to assess the performance of regression models. As shown in Tables 1 and 2, the Random Forest model performed exceptionally well on the dataset, achieving high accuracy. Consequently, the proposed distributed architecture utilizes the Random Forest model as both a pre-classifier and a regressor. The test data is applied to a pre-trained random forest pre-classifier model, which classifies the data into 8 classes. These class data are then applied to the respective pre-trained random forest regression models for BG estimation. Table 3 presents the performance analysis results of this distributed architecture, highlighting the effectiveness of using Random Forest for pre-classification and regression tasks.

Table 1 Comparing the performance of implemented pre-classification models. Bold represents the best testing results of a particular model.

Pre-classifier	Accuracy (%)	Precision	Recall	F1 score
KNN	74.77	0.74	0.75	0.73
SVM	80.9	0.81	0.81	0.80
DT	94.7	0.95	0.95	0.95
FCN	97.05	0.97	0.97	0.97
RF	**97.9**	**0.98**	**0.98**	**0.98**

Table 2 Comparison of performance evaluation results of implemented regression models. Bold represents the best testing results of a particular model.

Regression models	mARD (%)	MAD (mg/dL)	RMSE (mg/dL)
MLR	2.22	1.56	3.38
SVR	1.95	1.56	3.2
DT	1.26	1.17	2.1
RF	**1.01**	**0.77**	**1.78**
FC	3.72	1.03	2.35

Table 3 Performance analysis of proposed distributed architecture using RF model

	mARD (%)	MAD (mg/dL)	RMSE (mg/dL)
Distributed architecture	1.51	1.79	6.08

6.2.2 Clarke Error Grid (CEG) Analysis

The Clarke Error Grid (CEG) Analysis is the standard method used to evaluate the clinical accuracy of blood glucose monitors. This analysis plots measured glucose values against reference values, dividing the results into five specific zones (A–E) to assess patient risk. Unlike simple statistical correlation, the CEG distinguishes between acceptable errors, which fall into Zones A and B, and errors that could potentially lead to dangerous or erroneous treatment decisions, categorized as Zones C–E. Fig. 5 presents the CEG analysis of a distributed architecture implemented using RF. Fig. 5 indicates that all of the model's predictions fall within zones A and B of the CEG. This model is expected to deliver the desired output and will be utilized in clinical practice.

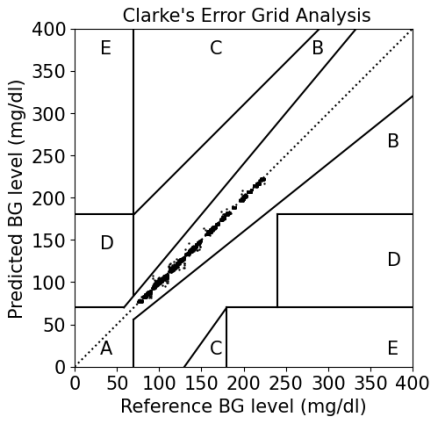

Fig. 5 CEG analysis of Distributed Architecture using RF

6.2.3 Performance comparison of proposed work with existing non-invasive approaches

Table 4 compares the proposed model with earlier non-invasive techniques, where a dash ("-") indicates values that are not recorded in the existing literature. In comparison to previous research, the proposed distributed model demonstrates outstanding measurement accuracy. The combination of regression and pre-classifier models produces strong results.

Table 4 Characteristic and statistical examination of proposed work with existing non-invasive approaches

Research works	mARD (%)	MAD (mg/dL)	RMSE (mg/dL)	CEG analysis	Data records	Measurement sample
Dai, et al. [29]	5.99	-	-	-	in-vivo	blood
Song, et al.[4]	8.3	-	-	Zone A & B	Human	blood
Pai, et al.[6]	3.09	11.5	15.65	Zone A & B	in-vivo	blood
Haxha, et al. [30]	-	-	33.49	Zone A & B	Human	blood
Jain, et al. [8]	6.65	12.67	21.95	Zone A & B	Human	blood
Joshi, et al. [31]	4.86	9.42	13.57	Zone A	Human	blood
Jain et al. [9]	12.5	-	-	Zone A & B	Human	blood
Joshi et al. [32]	5.34	8.3	12.7	Zone A	Human	Capillary & Serum
Sun et al.[33]	7.31	-	21.06	Zone A & B	Human	blood
Wei et al.[34]	-	11.33	-	Zone A & B	Human	blood
Proposed work	**1.51**	**1.79**	**6.08**	**Zone A**	**Human**	**blood**

6.3 DCRNet for BG forecasting

A new hybrid deep learning architecture, called DCRNet, has been proposed for predicting blood glucose (BG) levels. This innovative architecture sequentially combines dilated convolutional layers with long short-term memory (LSTM) layers, allowing it to effectively capture both local patterns and global temporal dependencies. DCRNet is trained and validated using in-silico data generated from the UVA/Padova T1DM simulator, as well as clinical data sourced from the OhioT1DM dataset. The proposed architecture consists of three layers of dilated convolutional

neural networks (DCNN), one LSTM layer, and two dense layers. The first three DCNN layers have 8, 16, and 32 neurons, respectively, with dilation rates (r) set to 1, 2, and 4. The LSTM layer contains 64 cells, while the two dense layers consist of 128 and 64 neurons, respectively, with a 30% dropout applied after each dense layer. To accurately forecast BG levels, the recent six BG samples are used. For a fair comparison with existing models, DCRNet utilizes continuous blood glucose levels, carbohydrate intake during meals, and insulin doses as input variables. The results of the DCRNet model are evaluated against various other models, including Multi-Linear Regression (MLR), Random Forest (RF), Decision Trees (DT), AdaBoost, XGBoost, Fully Connected Networks (FC), Convolutional Neural Networks (CNN), Dilated CNN (DCNN), Simple Recurrent Neural Networks (RNN), and LSTM. DCRNet is trained and validated using virtual patient's dataset generated from the UVA/Padova T1D Mellitus (T1DM) simulator and OhioT1DM dataset of real patients.

6.3.1 In-silico dataset and OhioT1DM dataset

In-silico dataset

Eleven adult simulated subjects are selected from the UVA/Padova T1D Mellitus (T1DM) simulator. Four daily meals: breakfast, lunch, snacks, and dinner, are planned with base carbohydrate amounts of 35g, 45g, 0g, and 50g, respectively. Each meal scenario is generated by adding 10g to the base values, with maximum carbohydrate limits set at 85g for breakfast, 105g for lunch, 30g for snacks, and 120g for dinner. This results in 1,344 meal scenarios simulated over one day. The dataset includes a time series of 1,440 blood glucose (BG) points recorded throughout the day for one adult for each scenario.

OhioT1DM dataset

The OhioT1DM dataset was created for the BG Level Prediction Challenge (BGLPC) and includes data from 12 individuals with T1D over eight weeks. Data were collected via CGM devices, fitness bands, and a smartphone app. Participants, aged 20 to 60, recorded their carbohydrate intake, stress levels, sleep quality, exercise, and illness symptoms. Fitness bands tracked heart rate, movement acceleration, GSR, skin temperature, and step count. BG levels were measured every five minutes, and insulin doses were noted. The dataset is available in two parts: training and testing sets.

6.3.2 Performance evaluation of BG forecasting models on virtual dataset of UVA/Padova T1DM simulator

Root Mean Square Error (RMSE) and Mean Absolute Error (MAE) are metrics used to assess the performance of forecasting models. Table 5 presents a comparison of the performance of BG forecasting models for in-silico subjects from the UVA/Padova T1DM. The proposed architecture

demonstrates the lowest RMSE except MLR and DCNN, as presented in Table 5. For simulated subjects, the RMSE values are 3.42 mg/dL, 6.45 mg/dL, and 17.73 mg/dL at prediction horizons (PH) of 15, 30, and 60 minutes, respectively. Additionally, DCRNet reports MAEs of 2.11, 4.47, and 11.78 mg/dL for simulated subjects across the same 15-, 30-, and 60-minute prediction horizons.

Table 5 Performance comparison of BG forecasting models for in-silico subjects of UVA/Padova T1DM simulator

Metrics	**Model name**	**Future Prediction Horizon (PH) (in minutes)**		
		15	**30**	**60**
RMSE (mg/dL)	MLR	3.06	6.24	17.55
	DT	4.39	8.19	21.5
	RF	3.84	7.16	19.19
	AdaBoost	11.09	17.19	31.05
	XGBoost	4.07	6.95	18.11
	FC	10.29	11.00	20.14
	CNN	9.82	8.36	17.88
	Simple RNN	7.25	8.87	23.27
	LSTM	7.37	7.76	17.56
	DCNN	2.87	5.54	17.88
	DCRNet (proposed)	**3.42**	**6.45**	**17.73**
MAE (mg/dL)	MLR	1.57	4.01	12.25
	DT	2.12	4.86	12.59
	RF	1.76	4.26	11.29
	AdaBoost	9.85	15.74	27.07
	XGBoost	2.72	4.64	12.93
	FC	7.93	7.8	12.8
	CNN	7.04	5.34	10.73
	Simple RNN	6.21	6.77	17.24
	LSTM	5.63	5.29	11.15
	DCNN	2.11	3.19	11.72
	DCRNet (proposed)	**2.11**	**4.47**	**11.78**

6.3.3 Performance evaluation of BG forecasting models on OhioT1DM real patients' dataset

Table 6 presents a comparison of the performance of BG forecasting models for the OhioT1DM dataset of real patients. The proposed architecture demonstrates the lowest RMSE, as presented in Table 6. For actual subjects, the RMSE values are 12.57 mg/dL, 20.72 mg/dL, and 34.41 mg/dL for the same prediction horizons. Additionally, DCRNet reports MAEs of 7.9, 14.13, and 25.5 mg/dL for actual subjects across the same 15-, 30-, and 60-minute prediction horizons. The comparison of RMSE and MAE results shows that the proposed DCRNet achieves superior

predictive accuracy, as evidenced by consistently lower RMSE and MAE than all implemented models. This architecture aids in predicting blood glucose (BG) levels in individuals with Type 1 Diabetes (T1D), allowing for timely corrective actions to regulate BG and prevent complications arising from hyperglycemia and hypoglycemia.

Table 6 Performance comparison of BG forecasting models for OhioT1DM real patients' dataset

Metrics	Model name	Future Prediction Horizon (PH) (in minutes)		
		15	**30**	**60**
RMSE (mg/dL)	MLR	13.1	22.19	35.84
	DT	18.64	31.14	49.31
	RF	13.1	21.82	35.51
	AdaBoost	32.05	37.5	44.75
	XGBoost	13.38	22.24	35.36
	FC	26.07	36.56	37.49
	CNN	38.94	33.22	40.08
	Simple RNN	16.6	23.6	40.16
	LSTM	14.17	21.21	35.6
	DCNN	12.80	20.83	34.30
	DCRNet (proposed)	**12.57**	**20.72**	**34.41**
MAE (mg/dL)	MLR	8.42	15.60	27.03
	DT	11.68	21.33	36.25
	RF	8.3	15.11	26.36
	AdaBoost	24.85	29.71	36.08
	XGBoost	8.72	15.7	26.53
	FC	19.80	26.91	28.56
	CNN	37.77	25.85	31.59
	Simple RNN	11.94	16.88	29.87
	LSTM	9.50	14.46	26.31
	DCNN	8.13	14.28	25.36
	DCRNet (proposed)	**7.9**	**14.13**	**25.50**

6.4 Intermittent Insulin Bolus therapy for T1D patients

6.4.1 Bolus insulin calculation

The traditional formula for insulin dosing uses the current glucose measurement (BG_t) to calculate bolus insulin for mealtime (BI_S), following the specific formula outlined in Eq. 3.

$$BI_S = \frac{CHO}{CR} + \frac{BG_t - BG_T}{CF} \quad (3)$$

Bolus insulin for mealtime is represented by BI_S. The variable CHO (g) indicates the amount of carbohydrates in the meal. Additionally, CR (in g/U) refers to the insulin-to-carbohydrate ratio, while CF (in mg/dL/U) represents the correction factor. Clinicians typically adjust these two

parameters through a trial-and-error process. The current blood glucose level is indicated by BG_t (in mg/dL), while the target blood glucose level is denoted by BG_T (in mg/dL).

Due to the natural delay between insulin administration and its peak metabolic effect, which occurs approximately 45 to 75 minutes later, reactive control often results in postprandial hyperglycaemia or hypoglycaemia. To address this issue, the proposed insulin dosage formula replaces the current glucose value with a predicted glucose level projected 60 minutes into the future. This adjustment allows for anticipatory control by forecasting the glucose level that corresponds to the peak activity of insulin. Consequently, the modified insulin bolus calculation formula is represented as MBI_S and is outlined in Eq. 4:

$$MBI_S = \frac{CHO}{CR} + \frac{\widehat{BG_{t+60}} - BG_T}{CF} \quad (4)$$

6.4.2 Simulation scenarios to test IIB therapy

This research utilizes virtual subjects generated by the UVA/Padova Type 1 Diabetes Simulator for all insulin calculations and to study the effect of insulin on glucose levels, rather than using real human participants. The UVA/Padova simulator is an FDA-accepted in silico platform designed for preclinical testing of insulin therapies and closed-loop control algorithms for Type 1 Diabetes Mellitus (T1DM). It provides a physiologically based simulation of glucose-insulin dynamics specifically for individuals with T1D. This tool allows researchers to design and test therapeutic strategies, such as artificial pancreas systems and closed-loop control, without exposing real patients to potential risks. To evaluate the performance of the proposed IIB therapy, ten adult in-silico subjects are utilized in the simulator. Four meals, breakfast (M_1), lunch (M_2), snack (M_3), and dinner (M_4), are planned for a single day to test the efficacy of the proposed multiple insulin dosage therapy. Meals are consumed at the following times: 8:00 AM, 12:00 PM, 4:00 PM, and 8:00 PM. The insulin dosage for each meal is calculated sequentially. The IIB therapy determines the insulin dosage based on forecasted BG values, carbohydrate (CHO) intake, and a current acting insulin (CAI). For the input BG samples, the most recent 6 values, measured at 5-minute intervals prior to the insulin dose, are used. In the current approach, previously administered insulin is not considered active in the body; therefore, the CAI is set to zero.

Four random meal scenarios are analysed to assess the impact of the calculated bolus insulin on BG levels. The four sample meal scenarios are as follows: Scenario 1 (S_1): [35, 45, 10, 50] grams, Scenario 2 (S_2): [45, 65, 15, 70] grams, Scenario 3 (S_3): [55, 90, 15, 90] grams, Scenario 4 (S_4): [55, 100, 20, 100] grams. Additionally, insulin can be administered at various times before a meal (e.g., 0, 15, or 30 minutes), which also affects BG levels. Consequently, four main scenarios are

used to generate different sub-scenarios based on the timing of the insulin injection relative to the meals. Table 7 presents ten sub-scenarios labeled from S_a to S_j. The columns S_I and M_{add} represent the sub-scenarios and the added meal, respectively. Columns M_1 to M_4 and M_{add} indicate the timing of insulin insertion before a meal. Sub-scenarios S_f to S_j are generated by omitting insulin for snack time, as the amount needed for 10 to 20 grams of carbohydrates is very low. During experimentation, it was observed that hypoglycaemic events might occur overnight. To mitigate this, an additional 20-gram meal is scheduled for 10:00 PM to prevent hypoglycaemia. The proposed intermittent insulin therapy is evaluated using 40 scenarios, which include four main scenarios and ten sub-scenarios. All 40 scenarios are simulated in the Uva/Padova simulator over a span of seven days.

Table 7 Illustration of different sub scenarios containing insulin insertion time before each meal

S_I	Insulin taken time before meal (minutes)				
S_i	M_1	M_2	M_3	M_4	M_{add}
S_a	0	0	0	0	No
S_b	30	30	30	15	No
S_c	15	15	15	15	No
S_d	30	30	30	30	No
S_e	30	30	30	30	Yes
S_f	30	30	No insulin	30	No
S_g	30	30	No insulin	30	Yes
S_h	30	30	No insulin	15	Yes
S_i	30	15	No insulin	15	Yes
S_j	15	15	No insulin	15	Yes

6.4.3 Evaluation of the proposed forecasted based IIB therapy

Many glycaemic control indicators are used in diabetes research. Among these, three key metrics measure the percentage of time spent in different glycaemic ranges [35]: Euglycemic Range (TIR): This range is defined as $70 \leq CGM \leq 180$ mg/dL, Below Range (TBR): This indicates levels where CGM is less than 70 mg/dL, Above Range (TAR): This indicates levels where CGM exceeds 180 mg/dL. Additionally, the Low Blood Glucose Index (LBGI) [36] and the High Blood Glucose Index (HBGI)[36] are utilized to assess the risk of hypoglycaemia and hyperglycaemia, respectively.

6.4.4 Analysis of intermittent insulin bolus therapy using TIR, TBR and TAR

To analyse the 40 insulin scenarios and their effects on 10 adults, we conducted a detailed examination focusing on S_a-S_j to identify the best sub-scenario. The mean, median, and interquartile range are calculated for each sub-scenario from the TIR, TBR and TAR values of all

ten adults across the main scenarios (S_1-S_4) to determine which sub-scenario is the best. Table 7 shows the mean, median, and interquartile range (IQR) for TIR, TBR, and TAR. The mean provides an estimate of the central tendency of the metrics. The median, on the other hand, offers a more reliable measure that is less influenced by extreme values, while the IQR represents the range in which the middle 50% of the data falls. Table 8 clearly shows that S_a is associated with worse-than-ideal glycaemic control, characterized by prolonged time spent outside the target range. On the other hand, S_f shows the highest TIR (mean= 98.86 %, median= 99.21 %, and IQR= 1.93 %), whereas S_g and S_h show reduced hypoglycaemia with the lowest TBR (mean= 0.01 %, median= 0 %, and IQR= 0%).

Table 8 Analysis of TIR, TBR and TAR

S_I	TIR (%)			TBR (%)			TAR (%)		
	Mean	**Median**	**IQR**	**Mean**	**Median**	**IQR**	**Mean**	**Median**	**IQR**
S_a	93.04	93.46	5.32	3.80	0.70	7.53	3.15	2.39	4.36
S_b	97.24	97.74	4.16	1.92	0.00	3.84	0.84	0.27	1.67
S_c	97.72	98.16	4.09	0.67	0.00	0.00	1.61	0.51	3.38
S_d	98.66	99.25	0.94	0.95	0.05	0.60	0.39	0.00	0.38
S_e	98.41	99.21	2.33	0.79	0.05	0.59	0.80	0.00	1.58
S_f	98.86	99.21	1.93	0.20	0.00	0.03	0.94	0.00	1.79
S_g	98.50	99.97	2.01	0.01	0.00	0.00	1.49	0.00	2.01
S_h	97.87	98.58	2.25	0.01	0.00	0.00	2.12	1.39	2.26
S_i	97.60	98.31	3.05	0.17	0.00	0.00	2.23	0.99	3.00
S_j	97.76	98.46	2.83	0.20	0.00	0.00	2.04	0.83	2.69

6.4.5 Analysis using LBGI, HBGI and BGRI

The mean, median, and interquartile range are calculated for each sub-scenario from the LBGI, HBGI and BGRI values of all ten adults across the main scenarios (S_1-S_4) to determine which sub-scenario is the best. Table 9 presents the analysis of LBGI and HBGI across various experimental sub-scenarios (S_a-S_j). It summarizes the mean, median, standard deviation (SD), and interquartile range (IQR) for LBGI, HBGI, and BGRI. The results indicate that S_g (Mean = 0.23, SD = 0.25) and S_h (Mean = 0.24, SD = 0.26) exhibit the lowest LBGI values, suggesting enhanced protection against hypoglycaemia. In the S_a-S_j comparisons, HBGI values are slightly higher than LBGI, with S_d showing the lowest risk of hyperglycaemia, which correlates with better glucose management (Mean = 1.08, SD = 0.53). When S_d and S_f are compared, it is found that S_f (Mean = 1.27, SD = 0.59) has a slightly higher HBGI but a lower LBGI. Significant differences in both central tendency and dispersion are observed when analysing BGRI across S_a-S_j. S_f and S_g have the lowest mean BGRI values (7.49 and 7.48, respectively), with relatively small variability (SD = 2.18 and 2.38, respectively). These sub-scenarios indicate that the BGRI results are steadier and generally lower.

Overall, S_f and S_g, which effectively balance hypoglycaemia (LBGI) and hyperglycaemia (HBGI), present the lowest total glycaemic risk based on this analysis.

Table 9 Statistical analysis of LBGI, HBGI and BGRI

Metrics		S_I									
		S_a	S_b	S_c	S_d	S_e	S_f	S_g	S_h	S_i	S_j
LBGI	**Mean**	1.76	1	0.75	0.8	0.72	0.46	0.23	0.24	0.35	0.4
	Median	1.08	0.53	0.51	0.45	0.56	0.28	0.14	0.16	0.29	0.34
	SD	1.48	1	0.71	0.84	0.62	0.47	0.25	0.26	0.35	0.39
	IQR	2.02	1.69	0.85	1.1	0.7	0.79	0.45	0.46	0.61	0.71
HBGI	**Mean**	2.25	1.28	1.6	1.08	1.4	1.27	1.57	1.58	1.6	1.64
	Median	2.15	1.24	1.6	1.07	1.11	1.2	1.3	1.4	1.61	1.69
	SD	0.77	0.59	0.62	0.53	0.79	0.59	0.89	0.73	0.64	0.61
	IQR	1.16	0.82	1.1	0.7	0.76	0.69	0.9	0.73	0.62	0.57
BGRI	**Mean**	14.6	9.28	9.21	9.67	10.54	7.49	7.48	9.22	9.52	9.68
	Median	13.92	9.18	9.11	9.35	9.71	7.26	6.36	8.52	8.89	8.84
	SD	5.99	3.35	2.69	4.91	4.85	2.18	2.38	3.13	3.35	3.7
	IQR	5.7	4.51	3.31	4.94	3.18	2.89	3.35	3.61	4.84	5.01

6.4.6 Analysis using CVGA

The overall accuracy and safety of glucose predictions for combined sub-scenarios (S_a-S_j) are evaluated using Control Variability Grid Analysis (CVGA) [37] for 10 virtual adults. CVGA graphs, created for each sub-scenario, plot subject-level minimum and maximum glucose estimates (2.5th and 97.5th percentiles) across four main scenarios (s1–s4) with five clinical zones (A–E). Zone A indicates precise glucose estimates; Zone B represents normal deviations with minimal clinical significance; Zones C to E represent increasing clinical error and potential harm. Fig. 6 shows the CVGA analysis for sub-scenarios (S_a-S_j). Adult blood glucose levels between 70 and 180 mg/dL are marked by blue dots, with levels outside this range shown in red. Table 10 lists the percentage of adults' BG levels in Zones A and B.

Most data points across all combined sub-scenarios are found in Zones A and B, indicating highly reliable glucose regulation. The overall accuracy in these zones has remained stable, between 85% and 100%. Notably, sub-scenarios S_f, S_g, and S_h achieved 100% of their data in these zones, showing minimal variance and optimal glycaemic control.

Sub-scenario S_f, which scored 75% in Zone A, demonstrated the highest accuracy in glucose predictions, reflecting an effective balance between insulin administration and carbohydrate intake. The adjusted insulin dosage in Sf results in a more stable glucose trajectory and fewer deviations from target ranges. In contrast, earlier sub-scenarios like S_a, with 85% in Zones A and B, showed slightly greater variability, likely due to insulin overlap or meal timing fluctuations.

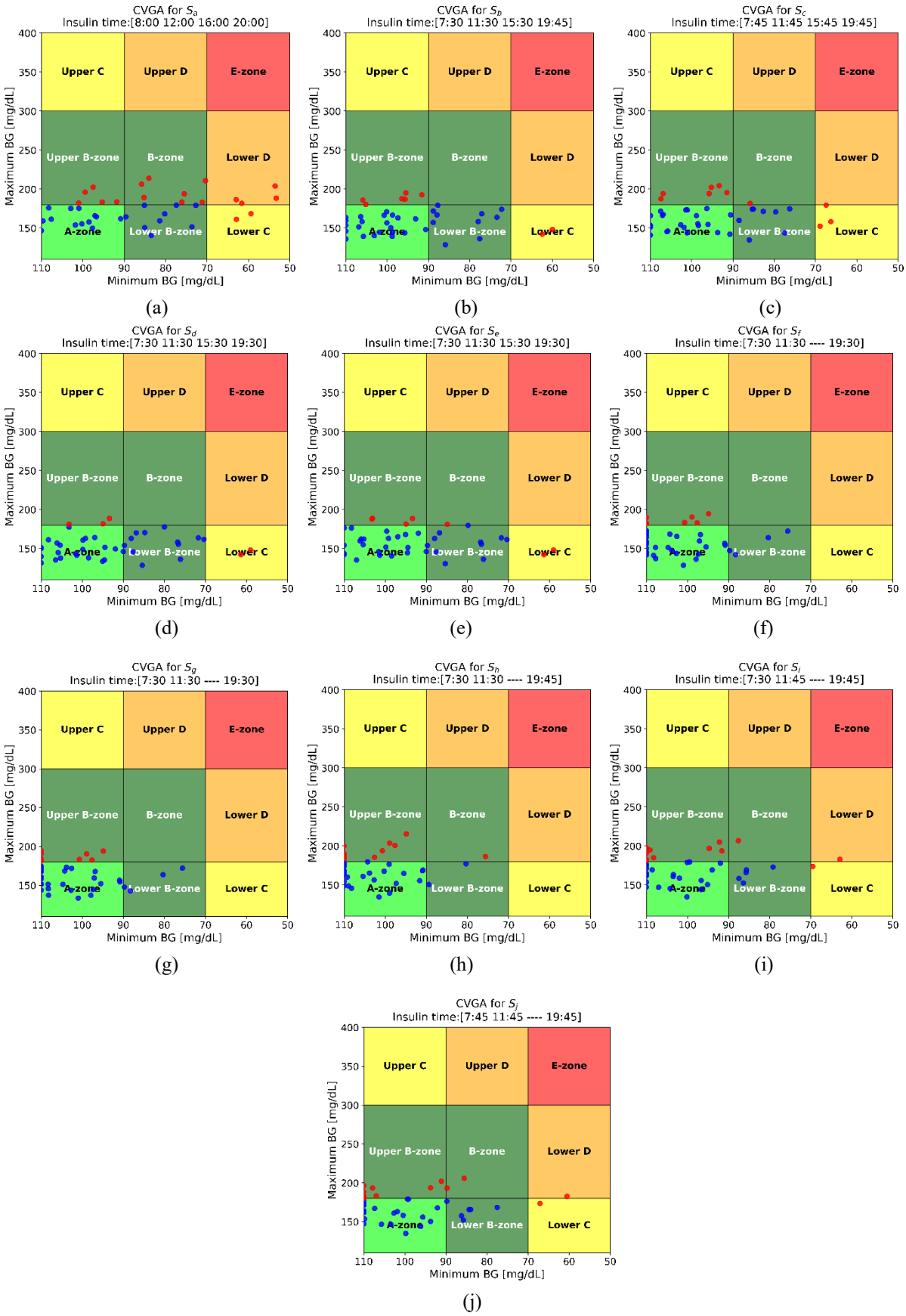

Fig. 6 CVGA analysis for sub-scenarios (S_a-S_j)

Table 10 The percentage value of adults' BG levels lies in zone A and Zone B in CVGA

S_I	Zone A (%)	Zone B (%)	Zone (A + B) (%)
S_a	32.5	52.5	85
S_b	55	40	95
S_c	55	37.5	92.5
S_d	60	35	95
S_e	57.5	37.5	95
S_f	75	25	100
S_g	70	30	100
S_h	65	35	100
S_i	55	40	95
S_j	52.5	42.5	95

7 Achievements with respect to objectives

This research successfully achieves its primary objectives by establishing a comprehensive, non-invasive continuous blood glucose monitoring system for managing Type 1 Diabetes. This system integrates precise blood glucose measurement, forecasting, and predictive insulin bolus therapy. A novel dataset of 784 individuals is created using a non-invasive device equipped with a 940 nm infrared sensor. The study identifies 13 critical features for blood glucose measurement by applying Shapley Additive Explanations (SHAP) to the collected data samples. A distributed architecture employing a Random Forest model is developed, achieving high accuracy in blood glucose measurement with a root mean square error (RMSE) of 6.08 mg/dL, a mean absolute difference of 1.79 mg/dL, and a mean absolute relative difference (mARD) of 1.5%. The research also introduces a hybrid DCRNet for forecasting, which combines multilayer dilated convolutional layers with an LSTM network. This design increases the receptive field without adding parameters or increasing computational cost, while effectively capturing dependencies over longer time series. The hybrid DCRNet enabled the development of a novel Intermittent Insulin Bolus (IIB) therapy. This proactive therapeutic approach calculates dosages based on predicted glucose levels rather than static ones, significantly outperforming conventional insulin bolus systems by achieving 99% Time in Range (TIR) across virtual cohorts and reducing the risk of hypo- and hyperglycaemia throughout the day. Furthermore, the system demonstrated exceptional safety, with all patient data remaining within Zones A and B of the Control-Variability Grid Analysis (CVGA). Ultimately, this research offers a simplified three-dose daily regimen, reducing patient dependence on a wearable insulin pump for insulin delivery throughout the day.

8 Conclusion

This research effectively addresses the limitations of invasive Continuous Glucose Monitoring systems and current static insulin dosage techniques. It establishes a strong foundation for accurately measuring real-time BG by integrating an innovative, non-invasive single-sensor device with an advanced machine-learning-based Distributed Architecture. BG forecasting is effectively performed using DCRNet in the proposed system.

The core contribution of this research is the development of the Intermittent Insulin Bolus (IIB) therapy, which utilizes forecasted glucose data to optimize insulin delivery. This predictive approach demonstrated exceptional clinical efficacy, achieving 99% of BG levels within the euglycemic range (70-180 mg/dL) and ensuring patient safety, as all the BG levels lie in zones A and B in the CVGA analysis.

Ultimately, this thesis proposes an effective, comprehensive, non-invasive CGM system for T1D that emphasizes glycaemic stability and reduces the need for a continuously attached insulin pump by suggesting only three bolus insulin doses (except snacks) each day, each taken at least 30 minutes before each meal. This thesis also offers a cost-effective, patient-friendly alternative to traditional Artificial Pancreas systems, significantly enhancing the quality of life for individuals with Type 1 Diabetes.

9 Copies of papers published and a list of all publications arising from the thesis

1. Ketan Lad, Maulin Joshi, and Amit Joshi, “Optical Sensor Based Continuous Blood Glucose Estimation Using Lightweight Distributed Architecture,” SN Computer Science, vol. 5, no. 8, Dec. 2024, https://doi.org/10.1007/s42979-024-03318-x.
2. Ketan Lad and Maulin Joshi, “DCRNet: Hybrid Deep Learning Architecture for Forecasting of Blood Glucose,” Journal of Electronics, Electromedical Engineering, and Medical Informatics, vol. 8, no. 1, pp. 53–68, Dec. 2025, https://doi.org/10.35882/jeeemi.v8i1.1245.
3. Ketan Lad and Maulin Joshi (2023). Continuous Blood Glucose Monitoring Using Explainable AI Techniques. In M. S. Raval, M. Roy, T. Kaya, & R. Kapdi (Eds.), Explainable AI in Healthcare. Chapman and Hall/CRC. https://doi.org/10.1201/9781003333425.
4. Ketan Lad and Maulin Joshi, “An intermittent insulin bolus therapy for improvement of personalized Type 1 diabetes management”. Paper is submitted to biomedical signal processing and control journal and currently under review.

10 Patents (if any): Not applicable

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