Deep Learning Ensemble for Predicting Blood Glucose Levels in Type 1 Diabetes Patients

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ABSTRACT

Anticipating Blood Glucose (BG) levels for patients can assist in averting hypoglycaemia and hyperglycaemia episodes beforehand. Therefore, to predict Blood Glucose (BG) values in Prediction Limits (PHs) of 15, 15, 30, and 60 minutes, this study suggests a predictive for blood glucose management using a deep learning algorithm. The model proposed by the author uses past Blood Glucose values congregated by devices used for constant monitoring of glucose as an endogenic feature and information about insulin administration(times) and carbohydrate intake as an exogenic factor. In this study, authors developed a predictive model for Type-1 diabetes using clinical parameters. The four prediction models were taken, which are subjected to a Bat Algorithm (BA) to optimize the weights using ensemble approaches and provide the ultimate predicted BG values. The model performance was rigorously evaluated using RMSE and loss function metrics to assess the accuracy and convergence. RMSE value of 0.082 was achieved, indicating a high level of precision for blood glucose level prediction; while the loss function stabilized at 0.0068, demonstrating the model's effectiveness in learning from the dataset. These results surpass current benchmarks and suggest that further refinement, such a model could significantly enhance the predictive monitoring of Type-1 diabetes. The findings in the paper indicate that the suggested model performs noticeably better than the baseline after applying four different algorithms for further optimization of results.

Keywords: Deep Neural Network, Deep Learning, Ensemble Learning, Feature Selection, Prediction Model, Type-1 diabetes.

I. INTRODUCTION

Millions of people around the world struggle with diabetes mellitus (DM), a metabolic disease with significant social and economic costs. This chronic condition arises from problems with blood sugar regulation, often leading to high blood sugar levels. Mainly there are two types of diabetes [29]: Diabetes Mellitus Type_1(T1DM) and Diabetes Mellitus Type_2(T2DM). In the paper, the focus is on the Type_2, where the most prevalent form occurs when the body either produces insufficient insulin or becomes resistant to its effects. While lifestyle changes are crucial for managing T2DM, medication may also be necessary [29][32].

Unlike Type-1, where the body lacks insulin, on the other side, T2DM people still produce insulin, but then again their body's cells resist its effects, leading to high blood sugar i.e. hyperglycaemia [1]. This insulin resistance can cause various complications, like headaches, lethargy, and even coma [32][33]. To manage their blood sugar effectively, these individuals typically require self-monitoring of blood glucose (SMBG), traditionally done through finger-prick tests. In recent years, various technologies have emerged to offer alternative, less invasive methods for blood sugar monitoring [2]. However, emerging from technological advancements, continuous glucose monitoring (CGM) represents a paradigm shift in blood glucose (BG) measurement for diabetic patients. Unlike traditional finger-prick methods, CGM utilizes skin-mounted sensors to measure BG continuously and provide real-time data at high resolution. This not only facilitates tighter BG control but also fuels research efforts aiming to predict future BG values, opening exciting avenues for personalized diabetes management [3]. Blood sugar (BG) levels aren't random; they follow a specific pattern. This predictability allows us to use historical data from continuous glucose monitoring (CGM) to forecast future BG values [4]. While traditional statistical methods were initially used in BG prediction models, they struggled to capture the complex, non-linear nature of BG fluctuations. Recent research has predominantly focused on machine learning models, which excel at handling such non-linear relationships [5-8].

While numerous studies used machine learning to predict blood sugar based solely on CGM readings, newer models show improved accuracy by incorporating additional factors like insulin intake and carbohydrate consumption [9]. Additionally, with Type-2 Diabetes (T2DM) making up over 90% of diabetes cases, research has shifted towards methods specifically tailored to its different underlying causes compared to Type-1 Diabetes (T1DM). This highlights the importance of considering both the data used and the specific type of diabetes for more effective BG prediction.

Blood sugar levels are influenced by multiple factors like stress, emotions, activity, insulin, and carbohydrates [31]. M.J. Sai et, al, 2022 works for Type-2 diabetes mellitus used five RNN models for prediction and a genetic algorithm is applied for weight optimization and results. The results were identified based on parameters like ReLu and Adamax. This variability makes it difficult to pinpoint the type of RNN algorithms which perform best [10]. The modified Long Short-Term Memory (LSTM) model, for example, may excel in some situations but struggle in others. To address this challenge, a Bat Algorithm (BA) is used to optimize the weights of an ensemble of different RNN models, tailoring them to specific combinations of influencing factors. For better results in T1DM author used sigmoid as activation and Adam rather than Adamax. This approach applied to T1DM data, utilizes four RNN algorithms to predict future BG levels for different aged people at different intervals (matching insulin and carbohydrate absorption rates) to prevent hypoglycemia and hyperglycemia. These prediction horizons align with common practices, allowing for easier comparison with other studies [10-15][30].

Based on the above discussion, the proposed research work is separated into various parts. Section 2 describes a review of the literature on diet recommendation systems conducted by various researchers. Section 3 highlights about proposed methodology its framework, description and process. Section 4 presents the experimental evaluation of the proposed model, assessing its performance in predicting blood sugar levels. Section 5 concludes the study which summarizes the key findings and offers recommendations for future research directions.

II. RELATED WORK

During early times finger stick was used for the self-tracking of Blood Glucose (SMBG) of diabetic patients to monitor fluctuations in their levels of blood glucose (BG) every few hours. Continuous_Glucose_Monitoring (CGM) systems, which deliver Estimated Glucose Values (EGV) regularly, has facilitated the collection of highly valuable data. This data collection has facilitated the creation of models for predicting BG levels and systems for early hypo-glycemia detection. CGM devices estimate glucose levels by measuring BG in the interstitial fluid, making them indirect methods. Consequently, regular SMBG tests are still necessary for periodic checks, and calibration of EGVs is crucial to enhance their accuracy. The precision of CGM devices, therefore, hinges on their calibration algorithms. Concerns regarding the clinical substitutability of EGVs for direct BG measurements have been explored by Rebrin et al [16]

A. Background

Numerous research efforts applied to focus on using data from Glucose Monitoring devices (CGM) which Continuously predicts future blood glucose (BG) levels. These predictions aim to manage and control BG levels efficiently to avert hypoglycaemia in diabetes patients, often employing alert systems. However, most of these studies have been conducted either in a controlled environment or through diabetic patients [17]. For an introductory survey of this research, Oviedo et al. provide a concise summary. [5]

The pioneering work by Bremer and Gough [4] demonstrated the feasibility of predicting future BG levels from historical CGM data, marking the beginning of numerous studies that applied both statistically traditional methods and modern machine learning techniques. Sparacino et al. [18] explored the prediction capabilities of a simple polynomial model versus an autoregressive (AR) model in a group of 28 T1DM patients, evaluating the models based on their prediction errors and the models' ability to capture the variability in BG levels.

Further advancements were made by Sun et al. [18], who employed the LSTM and Bi-LSTM model to analyze data from 26 T1DM patients, achieving notable accuracy in their predictions. Perez-Gandía and colleagues [20] utilized an artificial neural network in a small cohort of T1DM patients, demonstrating the network's effectiveness over several forecasting horizons.

Rabby et al. [21] introduced a sophisticated approach by combining a stacked LSTM framework with Kalman smoothing, processing eight weeks of data from T1DM patients to yield impressive predictive accuracy. Similarly, Li et al. [22] introduced a novel neural network convolutional-RNN (CRNN) model, tested on both simulated and real patient data, showcasing its potential with promising prediction errors at various forecasting intervals. These studies collectively underscore the potential of leveraging CGM data through advanced analytical techniques for better diabetes management.

B. Preliminaries

In this study, authors applied four algorithms based on RNNs at the initial stage to develop models for predicting blood glucose (BG) values. RNNs are a type of Artificial Neural Network (ANN) characterized by their hidden nodes connected in a cyclical pattern, enabling the network to process sequences of varying lengths flexibly. Despite their flexibility, RNNs encounter challenges with long-term dependencies, as the learning effectiveness decreases with increasing gaps between data points.

To address these challenges, LSTM networks introduced cell states within the traditional RNN architecture, mitigating the long-term dependency issue[24]. A stacked LSTM enhances this approach by adding multiple hidden layers, increasing the network's depth and potential for accuracy. Unlike standard RNNs that only utilize past data, bidirectional LSTMs also incorporate future data, further improving long-term dependency handling. The Gated Recurrent Unit (GRU) algorithm, with its update and reset gates, offers performance comparable to LSTM but with more efficient computations [25].

Furthermore, Bat Optimization Algorithms (BA) are employed for optimizing ensemble weights [32]. BA works by using behaviour of microbats which uses its echolocation values and perform global optimization:

These methodologies combined advanced neural network architectures and evolutionary algorithms to augment the efficiency and accuracy of BG prediction models in this research.

III. METHODOLOGY

This research introduces deep learning models for predicting blood glucose (BG) levels, categorized into univariate and multivariate models based on the input variables used. The univariate model relies solely on historical BG data, while the multivariate model incorporates additional factors such as carbohydrate (CHO) intake and the timing of insulin injections alongside past BG values. Although both models share the same structural design, their inputs vary. The comprehensive methodology for this work is illustrated in Figure shown below(Figure 1).

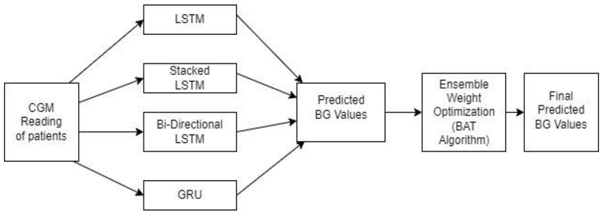

Fig.1. Prediction model for Blood-Glucose-Values

The methodology unfolds through several stages: gathering data, preprocessing it, forecasting time series with four RNN-based algorithms, and optimizing the ensemble weights using BAT Optimization Algorithms (GAs). The general steps to work are as follows:

Step1: Data Preparation: Initially, websites and databases were developed to enable the remote submission of data. Demographic details of diabetes patients, CGM data, as well as carbohydrate and consumption of insulin information, fed through a web interface and saved in the database table. Subsequently, this collected data was transformed into formats compatible with neural networks through a preprocessing step.

Step2: Prediction Model Development: The data which was fed as input data were organized based on the specified lookback period, which determines the sum of values considered in past, and the timestamp, indicating the sequence length. Data samples were arranged using a sliding window approach with a step size of one. A comprehensive illustration of the data structuring process for neural network compatibility is depicted in Figure 2, which includes terms defined as follows: "Lookback" refers to the time interval in minutes from which BG readings are taken as input; "prediction point" signifies the future time at which BG levels are forecasted, expressed in minutes post-horizon (PH); and "sampling rate" is the frequency at which BG readings are recorded, set at every 5 minutes.

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TABLE I
HYPER TUNING PARAMETER VALUES

Hyperparameter	Value
Lookback	5
Count of units	50
Group size	40
Transfer function	Sigmoid
Optimization Technique	Adam
Cost function	MSE
No. of iterations	250

Step 3: Optimization with Bat Algorithms: For the subsequent optimization phase (step 3), four distinct RNN-based algorithms were applied to generate BG value predictions. Each algorithm differs slightly in its approach, with specifics outlined in Table I, particularly regarding hyperparameters. These hyperparameters were finely tuned through an experimental process of trial and error to achieve optimal performance.

Step4: Optimization with Bat Algorithms (GAs): This stage focuses on the BAs based on the predicted blood glucose (BG) values generated by each RNN model from

Step5. The primary goal of employing BAs is to fine-tune each RNN model by optimizing the ensemble of weights. The fitness of each RNN's output is evaluated, leading to the identification of the optimal weight configuration through an objective function which aims to minimize the Root Mean Square Error (RMSE).

A. *Workflow*

To follow the baseline methods, the workflow of the proposed approach is shown below. Figure 2 represents a detailed explanation of the process used by the author. The workflow represents the workflow for a machine learning model that's designed for continuous glucose monitoring (CGM) in patients with Type 1 diabetes mellitus using four models along with an optimization algorithm. Each step contributes to refining the data and improving the predictive performance of the model:

- Input Diabetes Dataset: This is the raw data collected from the CGM devices which monitor the glucose levels of patients with Type 1 diabetes over a while.
- Data Cleaning: Given that real-world CGM data can be messy, this step likely involves removing outliers, errors, or irrelevant data points to ensure that the dataset is clean and ready for processing.
- Feature Selection: Here, you decide which features (e.g., historical glucose levels, time of day, meals, insulin doses) are most relevant for predicting future glucose levels. This is crucial for improving the model's accuracy and efficiency.
- Pre-Processing of Data: This phase includes several sub-steps to prepare the data for the LSTM model:
    - Min-Max Transformation: A common scale is set and the scaling technique adjusts the features to that scale without distorting differences in the ranges of values.
    - Ranging the data: This may involve setting specific ranges for the data, perhaps to match the input requirements of the LSTM model or to focus on specific glucose levels that are of clinical significance.

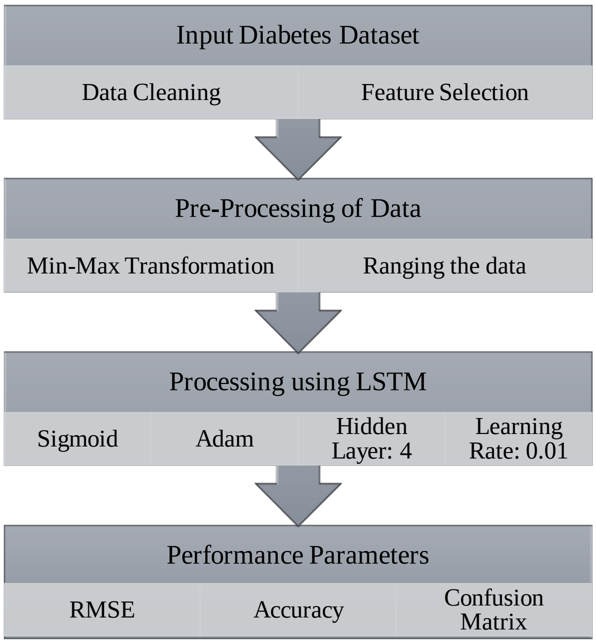

Fig.2. Workflow of the proposed approach

- Processing using LSTM: LSTM networks are mainly suitable for time-series data like CGM readings because they can learn and remember long-term dependencies. In this context:
    - Sigmoid: This is an activation function that's used within the LSTM gates to control the flow of information.

  - Adam: An optimization algorithm that adjusts the network weights iteratively based on training data to minimize prediction errors.
  - Hidden Layer: 4: Suggests that the LSTM has four layers deep, which allows the network to learn complex patterns in the time-series data.
  - Learning Rate: 0.01: This is a hyperparameter that governs the speed at which the network learns. A learning rate of 0.01 is a balanced choice that's neither too slow nor too fast.
- Performance Parameters: To evaluate the effectiveness of the LSTM model, several metrics are used:
  - RMSE (Root Mean Square Error): A common metric for regression problems. It's particularly useful for CGM since it can highlight large errors in glucose level predictions.
  - Accuracy: This might refer to the proportion of time, predicted glucose levels are within a certain range of the actual readings, which is important for clinical decisions.
  - Confusion Matrix: This is unusual for regression tasks like CGM prediction but could be used if the predictions are categorized (e.g., into hypo-, hyper-, or normal glycemic states).

This workflow supports the development of a robust predictive model for CGM in Type-1 diabetes patients, to provide accurate forecasts of glucose levels, allowing for better glycemic control and early warning of potential hypo- or hyperglycemic events.

A. Algorithm

To take the input data from the selected diabetes dataset from the public repository, the selected attributes are:

Sample_Number:	*Si*
Glycemic index value:	*HbA1c/ carbohydrate intake and insulin*
Factor to predict:	*Diabetic*

And the other key factors to determine the outcome are *Gender and Age.* Initially, the models used were the LSTM, Stacked LSTM, Bi-LSTM and GRU. For enhanced performance and understanding of the working of the proposed method, the modified LSTM is used. The algorithm to work on the proposed model is shown as Algorithm I.

Algorithm I: M-LSTM(Diabetes Dataset)

Step 1. Initialize the sample size with the dataset tuples i.e. *SN, sample size N* of the dataset

Step 2. Principal Component Analysis (PCA) is applied to get the selected attributes and the featured selection of *Si, Hb1Ac, and Diabetic,* which is further classified into the diabetic, pre-diabetic, and non-diabetic categories.

Step 3: Under the pre-processing method, the min-max transformation is applied to the tuples to get the ranged value to compute.

```
# Transformation
scaler = MinMaxScaler()
scaler.fit(x)
x = scaler.transform(x)
# reshape
x = x.reshape(x.shape[0], x.shape[1], 1)
```

Step 4: For the input *Si*, Modified LSTM is applied to sequences the outcomes and their long-range dependencies, using the Sigmoid Activation Function.

```
dense1 = LSTM(100, activation =
'Sigmoid')(input1)
```

Step 5: For the Hidden layers count 4, the learning rate is set to 0.01 with the Adam optimizer

```
keras.optimizers.Adam(learning_rate=0.01)
```

Step 6: Train the model and the Adaptive property of the proposed model holds the values and uses 50 epochs with successive LSTM approach.

The same algorithm is implemented in the next section and results are discussed on different epochs count.

IV. IMPLEMENTATION

This section delves into the experiments carried out the effectiveness of the derived predictive model. Initially, the dataset was acquired and subsequently pre-processed to ensure it was suitably formatted for the neural network, involving filtering and cleaning steps. By following this method, the evaluation of the model is in two distinct scenarios, differentiated by the type of input data used. Further, identify the models are anlyzed that focusing on the RMSE metrics. To further understand the disparities in predictive accuracy residual analysis, and CG-EGA were employed.

A. *Data Overview*

The dataset was sourced from the Dexcom G5 Mobile Continuous Glucose Monitoring (CGM) system, involving 51 hospitalized patients with Type-2 Diabetes Mellitus. The Dexcom G5 system comprises a sensor, transmitter, and mobile application. The device records glucose levels every 5 minutes throughout 4 to 7 days, with the sensor affixed to the patient's body, transmitting data to the mobile app receiver at consistent intervals. Data collection occurred at SoonChunHyang University-Cheonan-Hospital [27] from July 2019 to March 2021. The amassed data, including patient demographics, CGM readings, and insulin and CHO intake information, was stored in an APM (Apache-PHP-MySQL) based database, and then exported in CSV format for research purposes. The patient cohort information is detailed in Table 2.

Out of the initial 51 diabetes patients, 29 were eligible for inclusion in the multivariate models, having provided valid CHO intake and insulin administration data. Consequently, the analysis was structured as follows: (1) evaluating the univariate model using data from all 51 patients, (2) comparing the efficacy of the multivariate model against the univariate model with data from the subset of 29 patients, and (3) employing the Root Mean Square Error (RMSE) as the metric for model performance assessment, with further examination of the best and worst outcomes to elucidate the variance observed between the two groups.

B. *Data Preprocessing*

The main goal of preprocessing was to clean and convert the data into a format compatible with neural network models. Unlike simulated in silico data, the data for this study were derived from clinical settings, introducing the possibility of outliers due to errors in wireless device communication. Moreover, the variability in patient-recorded exogenous factors, such as carbohydrate (CHO) intake and insulin administration, necessitated meticulous preprocessing to ensure consistency and reliability. Initially, CGM readings obtained during the study were categorized as “low” for BG values under 60 mg/dL and “high” for those above 400 mg/dL. As a result, both the input CGM readings and the model's output predictions were calibrated to maintain a minimum of 60 and a maximum of 400 mg/dL. Furthermore, the direct patient input of insulin and CHO data was standardized by converting all entries to binary (0 or 1) values, addressing the variation in how patients reported their CHO intake and insulin usage. This approach was taken to simplify and standardize the representation of CHO and insulin data across patients. Lastly, time-series data, including timestamps for insulin and CHO entries, were integrated with historical BG values as part of the preprocessing effort.

C. *Results*

The results of experiments were conducted under two different setups based on the type of input data: univariate models, which utilize only glucose readings, and multivariate models, which incorporate additional Carbohydrate intake and administration of several times insulin alongside glucose monitoring data. The efficacy of these models was assessed and predicted over horizons of 15, 30, and 60 minutes post-horizon (PH), along with their performance benchmarked against an ARIMA model serving as the baseline[28]. Figure 3 shows the outcome as the loss function and RMSE on 20 epochs; whereas figure 4 shows the same on 50 epochs.

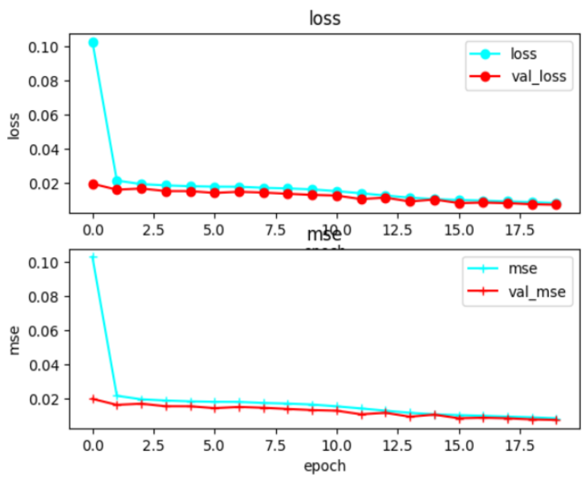

Fig.3. Loss and RMSE value at 20 epochs

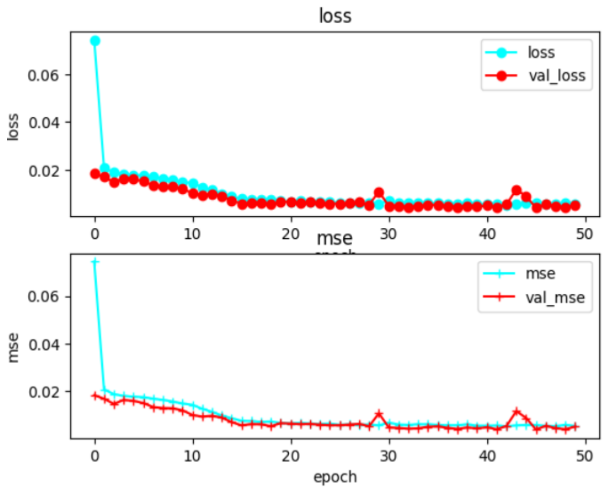

Fig.4. Loss and RMSE value at 50 epochs

The evaluation of the proposed models was based on two key metrics: Root Mean Square Error (RMSE) and Continuous Glucose-Error Grid Analysis (CG-EGA). RMSE is a widely recognized measure in regression analyses, providing a basis for performance comparison across various studies. CG-EGA, on the other hand, offers an evaluation of the clinical relevance of BG prediction models. It employs an error grid to categorize the accuracy of predicted versus measured BG levels into five zones, from A to E, with Zone A indicating the highest clinical accuracy. The distribution of prediction points closer to Zone A signifies more clinically relevant outcomes.

Univariate Model: Results Using CGM Data. In this segment, we explore the outcomes of applying a univariate model to CGM data from all 51 patients; where the model solely relies on CGM readings, excluding any external factors. The univariate model demonstrated superior performance with the lowest variability in its results. Notably, at prediction horizons of 15 and 30 minutes, the model's accuracy significantly surpassed that of the baseline model, as confirmed by a 5% level of statistical significance.

Multivariate Model: Multivariate Model Results Including Exogenous Factors. This section analyzes the performance of univariate and multivariate models based on data from 29 patients. Among the original 51, 29 diabetic patients qualified for multivariate analysis. For these patients, the RMSE values were 11.08 (3.19), 19.25 (5.28), and 31.30 (8.81) mg/dL for prediction horizons of 15, 30, and 60 minutes, respectively. In comparison, using the same patients' data in univariate models resulted in RMSEs of 11.28 (3.34), 19.99 (5.59), and 33.13 (9.27) mg/dL for the respective prediction horizons. The baseline ARIMA model had RMSE values of 14.82 (4.41), 23.11 (6.66), and 35.67 (10.23) mg/dL. Thus, both the univariate and multivariate models significantly surpassed the baseline, as shown by t-tests with a 5% significance level. Furthermore, the multivariate models demonstrated marginally better accuracy than the univariate models, and the analysis discusses potential reasons for this slight difference."

V. CONCLUSION

This research focused on developing highly accurate, individualized blood glucose (BG) prediction models for hospitalized patients diagnosed with Type 2 Diabetes, employing weight ensemble optimization through Genetic Algorithms (GAs) on the outputs from RNN-based algorithms. The innovative approach of optimizing an ensemble of models, each based on a different algorithm, using GAs, significantly enhanced model performance and robustness to data variability, rather than relying on a single-algorithm model. A notable limitation of this study was the inclusion of potentially imprecise data for exogenic factors such as carbohydrate intake and dosage information of insulin, attributed to the real-life conditions under which the data were collected and recorded. Consequently, the potential exists for multivariate models to exhibit substantially improved performance over univariate models in future research, provided that more accurately and rigorously collected data are utilized, even if the data volume remains constrained.

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