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Blood glucose prediction model for type 1 diabetes based on artificial neural network with time-domain features

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ABSTRACT

Predicting future blood glucose (BG) levels for diabetic patients will help them avoid potentially critical health issues. We demonstrate the use of machine learning models to predict future blood glucose levels given a history of blood glucose values as the single input parameter. We propose an Artificial Neural Network (ANN) model with time-domain attributes to predict blood glucose levels 15, 30, 45 and 60 min in the future. Initially, the model's features are selected based on the previous 30 min of BG measurements before a trained model is generated for each patient. These features are combined with time-domain attributes to give additional inputs to the proposed ANN. The prediction model was tested on 12 patients with Type 1 diabetes (T1D) and the results were compared with other data-driven models including the Support Vector Regression (SVR), K-Nearest Neighbor (KNN), C4.5 Decision Tree (DT), Random Forest (RF), Adaptive Boosting (AdaBoost) and eXtreme Gradient Boosting (XGBoost) models. Our results show that the proposed BG prediction model that is based on an ANN outperformed all other models with an average Root Mean Square Error (RMSE) of 2.82, 6.31, 10.65 and 15.33 mg/dL for Prediction Horizons (PHs) of 15, 30, 45 and 60 min, respectively. Our testing showed that combining time-domain attributes into the input data resulted in enhanced performance of majority of prediction models. The implementation of proposed prediction model allows patients to obtain future blood glucose levels, so that the preventive alerts can be generated before critical hypoglycemic/ hyperglycemic events occur.

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1. Introduction

Diabetes is a chronic disease that results in problems with blood glucose (BG) regulation. Diabetics cannot control their BG naturally due to the absence of insulin secretion (in Type 1 diabetes/ T1D) or defective insulin secretion and action (in Type 2 Diabetes/ T2D) [1,2]. Careful self-management of BG is required for diabetics otherwise they risk long-term complications such as hypertension and stroke [3–5]. To achieve a near-normal glucose metabolism, type 1 diabetics must administer insulin either via injection or insulin pump [6]. Monitoring blood glucose allows patients to avoid acute complications of type 1 diabetes, namely hypoglycemia and hyperglycemia [7]. Hyperglycemia is a condition in which an excessive amount of glucose circulates in the blood plasma (BG $>$ 180 mg/dL). Hyperglycemia can result in long-term complications, e.g., retinopathy [8,9], kidney disease [10,11], and cardiovascular disease [12,13]. Hypoglycemia, also known as low blood sugar, is a fall in blood sugar to levels below normal (BG $<$ 70 mg/dL) and it is associated with increased short- and long-term mortality [14–16]. Self-monitoring of blood glucose (SMBG) is an important component that helps type 1 diabetes (T1D) patients manage daily decisions related to food intake, insulin dose, and physical exercise. SMBG allows patients to measure their glycemic values multiple times in a day using a fingerstick blood glucose meter [17]. Recently, advances in sensor technologies has allowed patients to measure the glucose concentration with the help of Continuous Glucose Monitoring (CGM) devices and offers patients an alternative to traditional SMBG practice [18]. CGM systems are wearable medical devices that provide real-time measurements of subcutaneous glucose concentration almost continuously, e.g., every 1–5 min over several consecutive days [19–24]. Furthermore, with the help of prediction models, it is possible to forecast future blood glucose and generate alerts if hypoglycemia or hyperglycemia is in danger of occurring. Therefore, accurate prediction of blood glucose prevents T1D complications and improves the quality of life and health of patients who use it.

Considerable research efforts have been made toward the development of blood glucose prediction models. Data-driven modeling is one of the techniques that have been utilized to predict future blood glucose [25,26]. It works by utilizing information hidden in the input–output data (i.e. from CGM, insulin, meal intake, physical activity, etc.), without needing a priori knowledge about the relationship between them. These techniques is often supported by machine learning models, which have had significant success in extracting useful information from electronic health records, such as for predicting diabetes [27,28], hypoglycemia [29], acute kidney injury [30], cancer [31,32] and older adults' risk of fall [33]. Several variables, such as glucose level, insulin, meal, heart rate and physical activity, have been utilized as inputs to machine learning-based BG prediction and have shown positive results. One of the methods in machine learning that has been utilized by previous studies for BG prediction is Artificial Neural Networks (ANNs). These methods have shown positive results [34–38]. Other methods in machine learning that have been utilized by blood glucose prediction models with multiple inputs are support vector regression (SVR) [39,40], gaussian processes (GP) [41], autoregression (AR) [40] and eXtreme Gradient Boosting (XGBoost) [42]. All the machine learning-based methods above have shown good accuracy in predicting future blood glucose for various prediction horizons (PHs).

The fact that glucose prediction can be enhanced by using only the recent history from CGMs has been looked into in many previous studies. Machine learning models have been able to predict future BG levels given a history of blood glucose or using a CGM device as the single input. Sparacino et al. [43] demonstrated the use of a first-order autoregressive model to predict the next 30 min of blood glucose values, while Pérez-Gandia et al. [44] used an ANN with the last 20 min of BG values as the input to predict the blood glucose of 15 T1D patients. Wang et al. [45] combined several predictive models into a single framework. The proposed adaptive-weighted-average framework based on AR, ELM and SVR showed significantly enhanced results when predicting BG compared to single algorithms. More recent studies have also shown that CGM data can be utilized as the single input for an ANN-based prediction model. To improve prediction performance, the optimum number of features to use for each patient model were investigated [46]. Furthermore, to optimize the parameters of the prediction model, Hamdi et al. [47] demonstrated the use of a Differential Evolution (DE) algorithm to select a proposed SVR model's parameters. The results showed that optimal prediction can be achieved and this approach has outperformed other models. Finally, Martinsson et al. [48] demonstrated the long short-term memory (LSTM) technique to predict blood glucose levels. Their final models were trained using the previous 60 min of CGM data in order to make predictions 30 and 60 min into the future. The aforementioned studies showed that the feature extraction process impacts the performance of prediction models, therefore it is necessary to investigate the different types of input features that can be extracted from CGM.

A feature extraction process is required to generate attributes that a machine learning model can focus on in order to learn from the data, this is especially true for time series datasets. Advances in the development of the Internet of Things (IoT) has generated a huge amount of continuous time series sensor data that is received at speed from devices all around the world. While attempting to extract information from time series sensor data, previous studies have shown preprocessing techniques can be utilized to extract time-domain, frequency-domain and discrete-domain attributes [49]. One technique used for time-domain data is statistical metrics which can be used to extract basic signal information from raw sensor data. Statistical based features have been utilized as input attributes for prediction models and have shown significantly improved results in fault diagnosis [50–53], inventory management [54,55], human activity recognition (HAR) [49,56–59], occupancy estimation [60] and seizure detection [61]. Therefore, utilizing time-domain (statistical) features is expected to improve the performance of prediction models on time-series blood glucose data.

Previous studies have shown that recent histories from CGM can be exploited as single inputs for ANN-based blood glucose prediction models with high accuracy. In addition, time-domain (statistical) features also shown significantly

improved results from prediction models for IoT time series sensor data. Nevertheless, there has been no study on a BG prediction model that uses time-domain features for ANN model. Therefore, in this study an ANN-based prediction model that considers blood glucose levels as a single input and includes time-domain features as additional attributes is presented. Our challenge is to reduce the number of inputs (by utilizing CGM as single input) during training without reducing the forecasting accuracy of the prediction model. In addition, by utilizing time-domain attributes we expect the proposed model to generate enhanced predictions, i.e., lower RMSE blood glucose predictions. The proposed prediction model based on ANN will be utilized to predict blood glucose levels 15, 30, 45 and 60 min in the future. Finally, a performance evaluation will be carried out by comparing our method with other machine learning based prediction models.

The remaining sections of this paper are organized as follows. In Section 2, we present related works in the blood glucose prediction field. Section 3 contains our proposed blood glucose prediction model. In Section 4, the results of the study and a discussion are presented. In Section 5, we discuss several limitations and remaining challenges, and finally, concluding remarks are offered.

2. Related works

The previous studies on blood glucose prediction models are mentioned in Table 1. The literature mentioned in Table 1 describes the successful implementations of several methods for BG prediction that use various inputs, data pre-processing and datasets. The performance of the prediction models have been measured based on root means square error (RMSE) for each prediction horizon (PH). The BG prediction models can be grouped into two based on their input type: they are either BG prediction models with multiple inputs (e.g. CGM, insulin, meal intake, physical activity, etc.) or BG prediction models with a single input (e.g.CGM only). Machine-learning based algorithms such as ANN, SOM, SVR, GP, AR, XGBoost have shown significantly improved results in the past for predicting BG level using multiple inputs. Furthermore, there have also been successful demonstrations of machine learning models that predict blood glucose that use CGM as their single input, such as ANN, Adaptive-weighted-average framework, SVR and LSTM models. Therefore, in this paper we decided to use previous CGM values as the single input for our proposed prediction model. In addition, to improve the prediction accuracy, time-domain (statistical) features will be used as additional attributes in the proposed prediction model.

3. Material and methods

CGM devices have been utilized by type 1 diabetics to collect their blood glucose level data in real time. This real time data improves diabetes management by helping patients to better self-manage their condition. The collected BG data can be used to train a prediction model. Those predicted blood glucose values can then be presented to the users. In order to predict blood glucose, a machine learning model is utilized to learn from time series datasets. Fig. 1 shows the scenario of generating a prediction model using specific blood glucose data from each patient. First, during the data preprocessing stage, collected time-series blood glucose from CGM of each patient was filtered to reduce noise and then split into train and test sets. Previous studies revealed that several filtering methods have significantly improved results after removing noise (large spikes) from the dataset [43,44,62]. The feature extraction method is used to convert time series data into an input matrix X and an output vector Y. The training data is then used by the neural network model to learn the pattern from a set of paired inputs and desired outputs. Once the learning process is completed, the trained model is used to predict BG values, these are compared with the real values (ground truth) to calculate the model's performance.

3.1. Data preparation

During the feature extraction stage, the time series dataset is converted into a set of paired inputs and desired outputs. We used the "*direct method*" to perform the prediction of each horizon independently from other predictions [63,64]. The direct strategy learns independently H *and* models f_h

$$y_{t+h} = f_h(y_t, \ldots, y_{t-n+1}) + w \tag{1}$$

with $t \in \{n, \ldots, N-H\}$ and $h \in \{1, \ldots, H\}$ and returns a multi-step forecast by concatenating the H predictions. To carry out this direct strategy, the sliding window approach can be utilized for segmentation of the time series dataset, details in Fig. 2. In this example, the input data can be constructed by collecting windows with the size $n = 6$ as input data for learning and we predict the blood glucose for the next $h = 3$. In our study, the blood glucose data was collected every 5 min, therefore this prediction model used the last 30 min of historical data (as features) to predict the next 15 min of blood glucose. In Fig. 2, the windows (depicted by red lines) were collected and presented as an input matrix X, while the next 15 min of values (depicted by green lines) were used as an output vector Y. Finally, the collection of paired inputs and desired outputs is split into a training set and testing set.

Fig. 3 shows more details of the sliding window approach on the blood glucose time series dataset of a diabetes patient. The pairs of inputs-outputs are obtained by moving the window one time step ahead each time. There are two parameters that need to be considered here, the first is window size, n, and the second is step ahead prediction, h. Therefore, to predict the BG value an hour from now using the last 30 min of data, a new pair of inputs-outputs must be generated with the values of $n = 6$ and $h = 12$.

By following this procedure, a set of paired inputs and desired outputs can be generated so that the supervised learning model can learn from these inputs and desired outputs. We let G refer to the blood glucose (BG) sensor data of a patient and g_i refers to a particular sensor value in the set, where $g_i \in G$ and $i = 1,2,\ldots,N$. Parameter N represents total number of BG sensor data entries. Finally, given the list of BG data G, n previous values (or the window size) and the forecasting horizon, h, the input X can be derived by creating an $[(N-n-h+1) \times n]$ input data matrix

Table 1 – Related works.

Reference	Type of input	Pre-processing	Method(s)	Subject	Dataset Type	Mathematical Accuracy
Pappada et al. [34]	CGM, insulin, metered glucose levels, nutritional intake, lifestyle, and emotional factors		ANN	27 T1D patients	Real	75 min (RMSE 43.9 mg/dL)
Daskalaki et al. [35]	CGM and insulin	Normalization	ANN	30 T1D patients	In silico	30 min (RMSE 2.8–4.5 mg/dL), 45 min (RMSE 4.0–6.3 mg/dL)
Zecchin et al. [36]	CGM and meal.	Normalization, Bayesian smoothing	ANN	20 T1D patients	Real	30 min (RMSE 16.6 mg/dL)
Bertachi et al. [37]	CGM, insulin, meal, and physical activity.		ANN	6 T1D patients	Real	30 min (RMSE 19.33 mg/dL), 60 min (RMSE 31.72 mg/dL)
Zarkogianni et al. [38]	CGM and physical activity	Normalization	Self -organizing Map (SOM)	10 T1D patients	Real	30 min (RMSE 11.42 mg/dL), 60 min (RMSE 19.58 mg/dL), 120 min (RMSE 31.00 mg/dL)
Georga et al. [39]	CGM, insulin, meal, time and physical activity		SVR	27 T1D patients	Real	15 min (RMSE 5.21 mg/dL), 30 min (RMSE 6.03 mg/dL), 60 min (RMSE 7.14 mg/dL), 120 min (RMSE 7.62 mg/dL)
Georga et al. [41]	CGM, insulin, food intake and physical activities	Feature ranking based on Random forest (RF) was utilized to extract the optimal attributes.	Gaussian processes (GP)	15 T1D patients	Real	30 min (RMSE 5.6 mg/dL), 60 min (RMSE 6.3 mg/dL)
Xie et al. [40]	CGM, basal bolus insulin, meal, exercise, heart rate, air temp, etc.	Two strategies were considered, recursive and direct.	Autoregression with exogeneous inputs (ARX) and SVR	6 T1D patients	Real	Recursive strategy : ARX models, 30 min (RMSE 19.59 mg/dL). Direct strategy : SVR model, 30 min (RMSE 19.53 mg/dL)
Midroni et al. [42]	Self-reported features : Meals, finger stick glucose, stress, exercise, etc. Basis Peak : heart rate, GSR, skin temperature, etc. Pump features : basal, bolus doses, etc. CGM features : BG from CGM	XGBoost's feature importance was used to select optimal features.	XGBoost	6 T1D patients	Real	30 min (RMSE 16.21 mg/dL)
Perez-Gandia et al. [44]	CGM	Last 20 min of BG as features.	ANN	15 T1D patients	Real	15 min (RMSE 10 mg/dL), 30 min (RMSE 18 mg/dL), 45 min (RMSE 27 mg/dL)
Wang et al. [45]	CGM		Adaptive-weighted-average framework based on AR, ELM and SVR	10 T1D patients	Real	15 min (RMSE ± 10 mg/dL), 30 min (RMSE ± 19 mg/dL), 45 min (RMSE ±28 mg/dL)
Hamdi et al. [47]	CGM	Differential Evolution (DE) was used to optimize the parameter of SVR.	SVR	12 T1D patients	Real	15 min (RMSE 9.44 mg/dL), 30 min (RMSE 10.78 mg/dL), 45 min (RMSE 11.82 mg/dL), 60 min (RMSE 12.95 mg/dL)
Ben Ali et al. [46]	CGM	Optimized number of features (last minutes of BG) for each patient.	ANN	13 T1D patients	Real	15 min (RMSE 6.43 mg/dL), 30 min (RMSE 7.45 mg/dL), 45 min (RMSE 8.13 mg/dL), 60 min (RMSE 9.03 mg/dL)
Martinsson et. [48]	CGM	Last 60 min of BG as features.	LSTM	6 T1D patients	Real	30 min (RMSE 18.87 mg/dL), 60 min (RMSE 31.40 mg/dL)

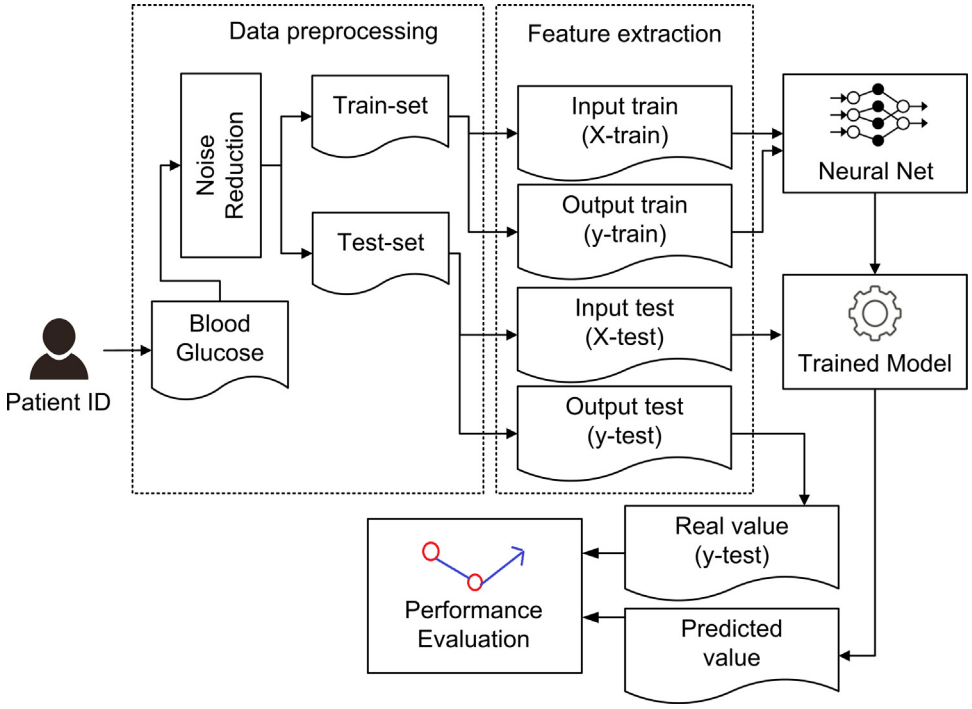

Fig. 1 – General schema for prediction model construction and evaluation.

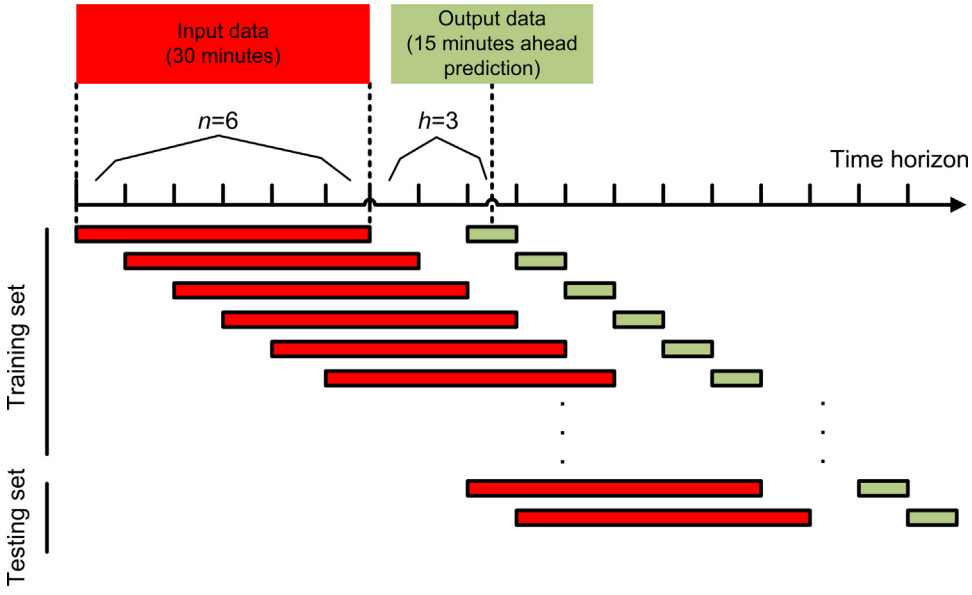

Fig. 2 – Segmentation of the time series dataset using the sliding window approach.

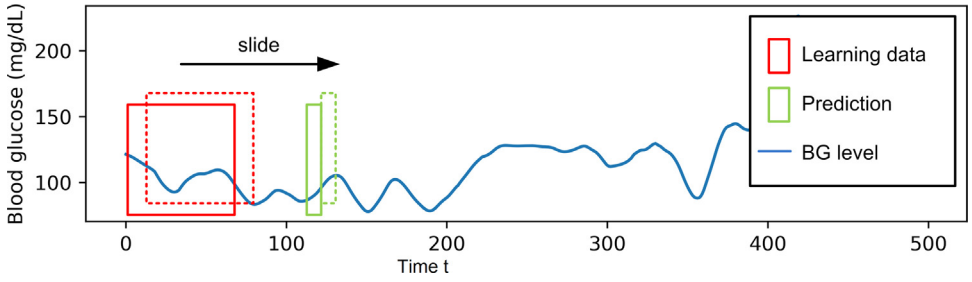

Fig. 3 – Sliding window approach for blood glucose data.

$$X = \begin{bmatrix} g_1 & \cdots & g_{n-1} & g_n \\ \vdots & \ddots & \vdots & \vdots \\ g_{N-n-h} & \cdots & g_{N-h-2} & g_{N-h-1} \\ g_{N-n-h+1} & \cdots & g_{N-h-1} & g_{N-h} \end{bmatrix} \quad (2)$$

and the $[(N-n-h+1) \times 1]$ output vector

$$Y = \begin{bmatrix} g_{n+h} \\ \vdots \\ g_{N-1} \\ g_N \end{bmatrix} \quad (3)$$

3.2. *Proposed time-domain feature and prediction model*

We utilize time domain (statistical) attributes as additional attributes for the n previous values, which are generated by the sliding window approach, such as minimum, maximum, mean, standard deviation, peak to peak amplitude (difference between highest and lowest), median, kurtosis and skewness [65]. These eight relevant statistical features extracted from each window S and s_i refers to the particular sensor values in the window where $s_i \in$ S and $i=1,2,\ldots, n$. The parameter n represents the total number of sensor data in a given window or window size. In our example there are six features being considered (n = 6 or the previous 30 min of BG values).

In the next step, the additional statistical features are combined with the n previous values generated by the sliding window approach. Finally, given the n previous values or window size, h the forecasting horizon, the 8 (eight) statistical features and N, the total data, the updated input X can be derived by creating the $[(N-n-h+1) \times (n+8)]$ input matrix:

$$X = \begin{bmatrix} g_1 & \cdots & g_{n-1} & g_n & min(g_1,\ldots,g_n) & \ldots & skew(g_1,\ldots,g_n) \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ g_{N-n-h} & \cdots & g_{N-h-2} & g_{N-h-1} & \cdots & \ldots & skew(g_{N-n-h},\ldots,g_{N-h-1}) \\ g_{N-n-h+1} & \cdots & g_{N-h-1} & g_{N-h} & \cdots & \ldots & skew(g_{N-n-h+1},\ldots,g_{N-h}) \end{bmatrix} \quad (4)$$

In this study, we employed a Multilayer Perceptron (MLP) model to predict blood glucose. The MLP is a class of feedforward ANNs with one input layer, one or more hidden layers, and one output layer. A backpropagation algorithm is utilized to train the MLP [66,67]. Our network is fully connected, so each unit receives connections from all the units in the previous layer. This means each unit has its own bias, and there is a weight for every pair of units in two consecutive layers. Net input was calculated by multiplying each input and its corresponding weight, and then summing. Each unit in the hidden layer took a net input and then applied an activation function. Therefore, given input units as x_j, output unit as y, units in the lth hidden layer denoted as $h_i^{(l)}$, φ as activation function, the network computation can be written as follow:

$$h_i^{(1)} = \varphi^{(1)}\left(\sum_j w_{ij}^{(1)} x_j + b_i^{(1)}\right) \quad (5)$$

$$h_i^{(2)} = \varphi^{(2)}\left(\sum_j w_{ij}^{(2)} h_j^{(1)} + b_i^{(2)}\right) \quad (6)$$

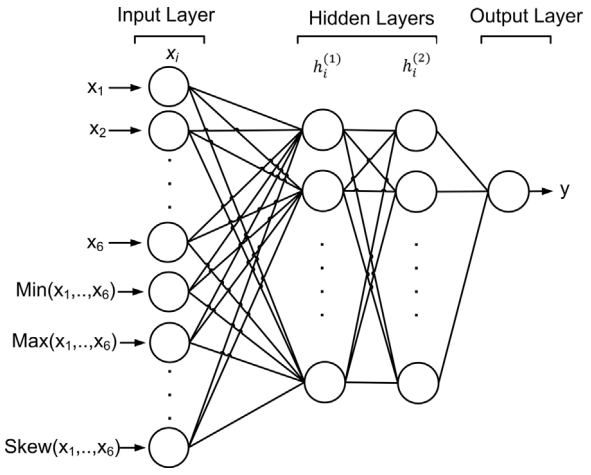

Fig. 4 – Proposed MLP model to predict future blood glucose.

$$y_i = \varphi^{(3)}\left(\sum_j w_{ij}^{(3)} h_j^{(2)} + b_i^{(3)}\right) \quad (7)$$

Back propagation compares the prediction result with the target value and modifies the weights for each training tuple to minimize the mean squared error between prediction and target values. This process was iterated multiple times to produce optimal weights, providing optimal predictions for the test data. Fig. 4 shows the proposed MLP model for predicting blood glucose given the input of the last 6 points of blood glucose and the extracted 8 statistical attributes.

We utilized the grid search algorithm [68] to automatically select the best parameters for the proposed MLP model. We applied the grid search for training set and measured by cross-validation to obtain the best predictive model, details can be seen in the flowchart in Fig. 5. The objective of this method is to select the parameter which generates the lowest prediction error (MSE) for the proposed blood glucose prediction model based on MLP. Finally, we found that the two hidden layer network with 100 neurons each, rectified linear unit (*ReLu*) as activation function and *Adam* as solver for weight optimization were the best parameters. In addition, grid search

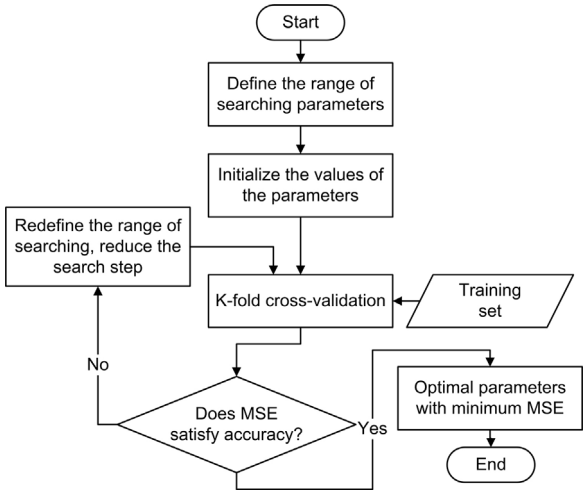

Fig. 5 – Flowchart of the grid search algorithm.

Table 2 – Distribution of blood glucose dataset.

No	Patient ID	Period (≈days)	#data point	Blood Glucose Levels (mg/dL)			
				Min	Max	Mean	Standard Deviation
1	19	9	2720	48	400	183	83
2	11	8	2393	49	374	175	53
3	13	7	2298	56	400	194	81
4	32	7	2231	40	391	159	77
5	4	7	2212	54	304	151	53
6	22	7	2173	40	232	122	38
7	16	7	2159	56	333	148	59
8	15	7	2145	66	353	179	58
9	18	7	2132	50	400	161	72
10	8	7	2097	44	364	160	67
11	6	7	2087	60	400	208	75
12	21	7	2076	53	400	158	72

approach revealed the L2 penalty (regularization term) parameter or alpha was 0.0001, learning rate was constant with 0.001 as its initial and maximum number of iterations was 1000. We applied these parameters for our proposed prediction model to all T1D patients in the dataset.

The proposed prediction model was used with the CGM dataset from DirecNet [69]. The clinical data set used in this study is publicly available online (https://public.jaeb.org/direcnet/stdy/167). The data were collected with informed consent from eligible subjects. The protocol was approved by DirecNet, Jaeb Center for Health Research. In order to carry out an accurate performance assessment, we use a clinical database derived from 12 subjects. The subjects are all children with diabetes type 1. The Guardian-RT device (i.e., a continuous glucose monitoring device) was used by the patients to record their blood glucose. The blood glucose data was collected every 5 min for approximately 7 days. In this study, we selected blood glucose measurement from the top 12 patients in terms of the highest number of data points. The detailed dataset distribution can be seen in Table 2.

At the data cleaning stage, each signal with missing data was imputed through spline interpolation to achieve a complete history of blood glucose levels. In addition, since noise in the dataset can decrease the accuracy of the prediction model, we used the Savitzky – Golay technique to filter noise from the blood glucose data of each patient [70]. We followed a previous study [62] by utilizing the Savitzky-Golay filter with a first order of polynomial and a filtering window of 15 steps to extract the smoothed data from the original CGM data. The holdout method was used for model evaluation where each patient's dataset is split into two parts: the first 80% for training and the rest for testing. The features of the data were normalized using min-max scaling. The forecasting models were implemented in Python V3.7.3, Xgboost V0.90, Scipy V1.3.2 and Scikit-learn V0.22.1 [71]. To simplify implementation of other machine learning models, we used the default parameters provided by Xgboost and Scikit-learn. The performance metrics of the forecasting models are the Root Means Square Error (RMSE), Mean Absolute Percentage Error (MAPE) and Coefficient of Determination (R^2). RMSE can be utilized to measure how large an error there is between the predicted and actual values, while MAPE measures the size of the error in percentage terms. Coefficient of Determination is defined as the square of the correlation (R) between predicted and observed values. Thus, it ranges from 0 (absence of correlation) to 1 (complete correlation). Furthermore, we used glucose-specific metric introduced by Favero et al. [72], called gMSE that applied specific penalty function to the Mean Squared Error (MSE). Given the reference value of blood glucose y, predicted value $\hat{y}$ and penalty function *Pen*, the gMSE can be presented as follow.

$$gMSE = \frac{1}{N}\sum_t (y_t - \hat{y}_t)^2 \, Pen\,(y_t, \hat{y}_t) \tag{8}$$

The penalty function divides the $(y, \hat{y})$ space in three regions, namely as Zone D1, D2 and D3 where different penalty values are applied for each zone. The idea of this metric is to penalize an overestimation in hypoglycemia and an underestimation in hyperglycemia. The D1 represents the condition when hypoglycemic (≤ 70 mg/dL) episode is happening and the prediction output are overestimating the real BG ($\hat{y} > y$). The D2 is when hyperglycemic (≥ 180 mg/dL) condition occurs to patient and the prediction output are underestimating the real BG ($\hat{y} < y$). Finally, Zone D3 covers remaining part of the $(y, \hat{y})$ space. It includes the euglycemia (70 mg/dL ≤ y ≤ 180 mg/dL) condition of patient, regardless of the predicted output ($\hat{y}$); patient is hypoglycemic (≤ 70 mg/dL), but actual BG is underestimated ($\hat{y} < y$); and hyperglycemic condition (y ≥ 180 mg/dL), but actual BG is overestimated ($\hat{y} > y$).

4. Results and discussion

4.1. *The performance of prediction models*

The proposed MLP model was applied to a CGM dataset and showed positive result for reducing prediction error as compared to other models. Table 3 shows the average and its standard deviation of RMSE from the forecasting models' prediction of blood glucose for various prediction horizons (PHs). We selected other data-driven algorithms that have been widely accepted in the data science community and have a proven track record for accuracy and efficiency for the comparison. Therefore, the proposed Multilayer Perceptron (MLP) model was compared with Support Vector Regression

Table 3 – Performance comparison of prediction models.

Model	Metrics	Prediction Horizon (minutes)			
		15	30	45	60
SVR	RMSE (mg/dL)	13.13 ± 17.30	17.86 ± 16.97	22.68 ± 16.99	27.08 ± 17.29
	MAPE (%)	5.58 ± 3.73	8.55 ± 3.95	11.73 ± 4.68	14.69 ± 5.36
	gMSE	893.90 ± 2635.09	1089.94 ± 2839.52	1373.36 ± 3096.21	1713.10 ± 3413.85
	R^2	0.88 ± 0.22	0.80 ± 0.22	0.68 ± 0.23	0.52 ± 0.26
KNN	RMSE (mg/dL)	6.03 ± 2.78	11.81 ± 4.54	18.86 ± 6.99	26.32 ± 9.53
	MAPE (%)	2.98 ± 0.57	6.13 ± 1.25	10.01 ± 2.19	14.22 ± 3.31
	gMSE	66.19 ± 102.40	228.08 ± 283.12	571.23 ± 668.24	1102.97 ± 1251.37
	R^2	0.98 ± 0.01	0.91 ± 0.04	0.75 ± 0.11	0.51 ± 0.22
DT	RMSE (mg/dL)	7.87 ± 3.79	15.04 ± 3.46	23.35 ± 6.36	32.86 ± 8.81
	MAPE (%)	3.83 ± 0.66	7.89 ± 1.31	12.40 ± 2.41	17.63 ± 4.13
	gMSE	111.86 ± 182.54	304.75 ± 199.55	777.19 ± 651.52	1473.29 ± 1056.33
	R^2	0.96 ± 0.02	0.84 ± 0.07	0.60 ± 0.17	0.19 ± 0.37
RF	RMSE (mg/dL)	5.06 ± 3.27	10.68 ± 4.35	17.72 ± 6.84	24.65 ± 9.56
	MAPE (%)	2.43 ± 0.64	5.52 ± 1.12	9.34 ± 1.86	13.29 ± 2.90
	gMSE	58.19 ± 122.24	188.67 ± 254.49	509.35 ± 655.19	1011.97 ± 1319.04
	R^2	0.98 ± 0.01	0.92 ± 0.04	0.78 ± 0.10	0.57 ± 0.19
AdaBoost	RMSE (mg/dL)	7.37 ± 3.09	14.56 ± 6.72	22.44 ± 9.05	28.78 ± 10.41
	MAPE (%)	4.12 ± 1.08	8.60 ± 2.82	13.66 ± 4.44	18.14 ± 6.27
	gMSE	92.42 ± 131.15	378.53 ± 565.31	824.51 ± 1073.90	1355.31 ± 1464.03
	R^2	0.96 ± 0.02	0.86 ± 0.08	0.64 ± 0.23	0.38 ± 0.42
XGBoost	RMSE (mg/dL)	5.42 ± 3.35	10.79 ± 4.88	17.20 ± 7.71	23.49 ± 10.17
	MAPE (%)	2.74 ± 0.71	5.74 ± 1.20	9.42 ± 2.34	13.18 ± 3.34
	gMSE	64.13 ± 131.10	205.08 ± 309.59	517.56 ± 742.77	949.48 ± 1304.08
	R^2	0.98 ± 0.01	0.92 ± 0.04	0.80 ± 0.09	0.62 ± 0.17
Proposed Model	RMSE (mg/dL)	2.82 ± 1.00	6.31 ± 2.43	10.65 ± 3.87	15.33 ± 5.88
	MAPE (%)	1.52 ± 0.42	3.46 ± 1.06	5.89 ± 1.50	8.69 ± 2.58
	gMSE	11.17 ± 8.64	57.70 ± 46.18	164.88 ± 134.90	343.02 ± 279.67
	R^2	0.99 ± 0.00	0.97 ± 0.02	0.91 ± 0.05	0.82 ± 0.11

(SVR), K-Nearest Neighbor (KNN), C4.5 Decision Tree (DT), Random Forest (RF), Adaptive Boosting (AdaBoost), eXtreme Gradient Boosting (XGBoost).

We followed previous studies that used the last 30 min of BG data as input and that demonstrated the existence of a strong dependency between the most recent 30 min of BG data and the values in the near future [39,41,73]. Therefore, in this study a window size $n = 6$ (last 30 min) was utilized for the machine learning models to predict blood glucose (BG) values. An individual prediction model was generated for each patient and the performance average was computed over the 12 models (generated from 12 patients). Time-domain features were utilized by the proposed MLP model as additional attributes (see formula 3 and 4), while other prediction models only utilized the last 30 min of values generated by the sliding window approach (formula 2 and 3). The proposed MLP model showed the highest performance by generating the lowest RMSE, MAPE and gMSE compared to other prediction models. The RMSE of the proposed MLP are 2.82, 6.31, 10.65 and 15.33 mg/dL for prediction horizons (PHs) of 15, 30, 45 and 60 min, respectively. In addition, the proposed model also generated the highest R^2 (coefficient of determination) compared to other models, they are 0.99, 0.97, 0.91 and 0.82 for PHs of 15, 30, 45 and 60 min, respectively. Finally, the results showed that as the prediction horizon increased, all prediction models generated higher RMSE, MAPE and gMSE but with lower R^2.

Table 4 presents the RMSE (mg/dL) and gMSE of the proposed MLP for each patient and for different PHs. These results show that each patient model generated different prediction results. For all patients, as the prediction horizon (PH) increased, the proposed model generated higher RMSE and gMSE. The combination input of the last 30 min of BG values and time-domain features were good enough for short term forecasting (i.e. 15 min). However, for longer term forecasting (i.e. 60 min), some of the prediction models from the small group of patients generated higher RMSEs and gMSEs compared to others, such as in patients 32, 18 and 6. The differences in lifestyle, meal intake and insulin injection (timing, dose, etc.) will affect the different pattern of BG dataset for each patient. Furthermore, previous study has applied the customized BG input (different window sizes) for each patient and the prediction performance was significantly improved [46]. Therefore, applying customized BG input for each patient in our dataset is expected to improve the performance of proposed prediction model, especially for this small group of patients (patients 32, 18 and 6).

As highlighted in Fig. 6, the predicted value from patient 21 is presented and compared with the original BG. The prediction output from the proposed MLP model are closer to the real/ original data, especially with a PH of 30 min (Fig. 6a). However, as the prediction horizon (PH) increases (Fig. 6b), the proposed forecasting model generates higher prediction errors. We can conclude that the results show that the proposed MLP is very promising and could be applied for blood glucose prediction in the real world.

To obtain prediction results from machine learning models, it requires huge efforts in term of data preparation and trained

Table 4 – RMSE (mg/dL) and gMSE of proposed model for different prediction horizons (PHs).

Patient ID	Prediction Horizon (min)							
	15		30		45		60	
	RMSE (mg/dL)	gMSE	RMSE (mg/dL)	gMSE	RMSE (mg/dL)	gMSE	RMSE (mg/dL)	gMSE
19	1.91	3.94	5.04	27.93	8.03	67.94	12.49	165.15
11	2.53	8.14	5.91	54.53	10.38	163.04	15.87	361.21
13	2.63	7.05	4.77	24.18	8.90	83.98	12.01	161.03
32	4.72	24.93	11.32	140.92	16.88	328.71	26.65	804.13
4	3.18	11.37	7.52	70.08	11.67	161.98	15.30	299.11
22	2.38	5.68	5.36	28.78	8.33	69.42	11.68	136.37
16	2.75	10.65	5.62	40.59	10.25	126.42	14.74	268.96
15	1.65	2.93	3.52	14.76	5.93	43.61	8.41	84.87
18	3.83	25.65	7.58	110.19	14.82	430.02	20.49	822.38
8	2.44	6.01	4.74	22.81	8.06	64.89	12.16	156.16
6	4.45	25.69	10.72	144.60	18.29	398.13	26.08	792.29
21	1.42	2.03	3.61	13.03	6.22	38.70	8.03	64.55

model generation. First, time-series blood glucose data for each patient needs to be presented into a set of paired inputs and desired outputs, so that individual/ personalized trained machine learning models can be generated by learning from input training set. Finally, future value of blood glucose can be presented by trained machine learning models for different prediction horizon. However, since slow changes of blood glucose level might be occurred in each patient, therefore the short-term blood glucose changes (i.e. next 15 min) might not be different than current blood glucose value. Based on this assumption, the simple model can be obtained with consideration that the future value of blood glucose is equal to the current value, so that it can reduce computational cost. Given the current value of blood glucose g_t and future value g_{t+h} for prediction horizon h, the prediction output of simple model can be presented as follow.

$$g_{t+h} = g_t \tag{9}$$

Fig. 7 showed the performance comparison between proposed model and simple model in term of RMSE (mg/dL) and coefficient determination (R^2). The proposed model generated lower RMSE (Fig. 7a) and higher R^2 (Fig. 7b) as compared to the simple model for all prediction horizon (PHs). As the prediction horizon increased, both models generated higher RMSE but with lower R^2. Furthermore, as prediction horizon increased, accuracy of simple model is lower as compared to the proposed model (Fig. 7b). The result showed that proposed model can be utilized for BG forecasting, so that the prediction error can be minimized.

4.2. *The impact of additional time-domain features on prediction error*

Table 5 presents the RMSE of the prediction models with different feature types for different PHs. The results show that by combining the input of the last 30 min of BG values and the time-domain features lower RMSE for all PHs were achieved as

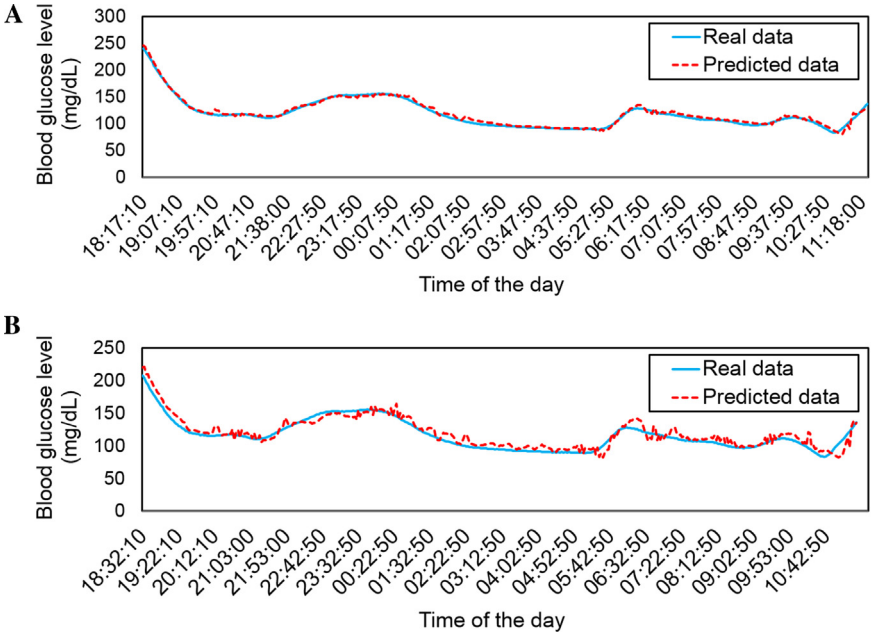

Fig. 6 – Prediction of blood glucose levels from patient 21 with different prediction horizons: (a) 30 min; (b) 60 min.

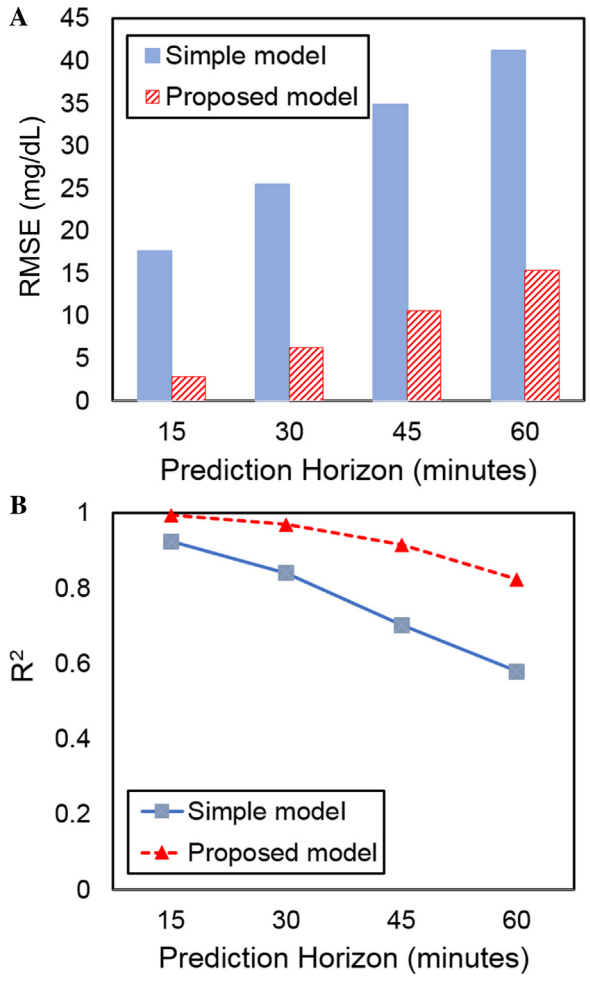

Fig. 7 – Performance comparison between proposed model and simple model for different prediction horizon based on: (a) RMSE (mg/dL); (b) R^2.

compared to prediction models with sliding window-based attributes (last 30 min) only, except for SVR (15 min, 30 min, 45 min and 60 min PHs), KNN (15 min and 30 PHs), AdaBoost (15 min PH) and DT (30 min PH). For longer term forecasting (i.e. 60 min), a combination of standard and time-domain features generated lower RMSE as compared to models with sliding window-based attributes, except for SVR. In our experimental results, the SVR, DT and AdaBoost models generated higher prediction errors for longer term forecasting compared to the other models, since we only used the default parameters provided by the Scikit-learn library. Therefore, optimizing parameters for all prediction models could be utilized in the future to improve their prediction performance. This advanced hyperparameter optimization has been applied in a previous study [47] that used differential evolution (DE) to enhance the performance of the SVR model.

Utilizing additional time-domain features has shown significant improvement on Multilayer Perceptron (MLP) as compared to other machine learning models, especially for long-term prediction (i.e., 60 min). MLP with additional time-domain features has reduced the RMSE as much as 0.71, 1.41, 1.95, 3.39 mg/dL for PH 15, 30, 45, 60 min, respectively. The result also showed that as increasing prediction horizon (PH), the time-domain based MLP generated higher reduction on RMSE as compared to sliding-window based MLP model. Finally, by integrating the sliding window approach and time-domain features as attributes for prediction models, the average of RMSE from the prediction models was reduced by as much as 0.16 and 1.46 mg/dL for PH 30 and 60 min, respectively, as compared to prediction models that used sliding window-based attributes only.

4.3. *Comparison with some previous studies*

To better predict blood glucose levels, several additional inputs have been proposed in previous studies, these include glucose level, insulin, meal, heart rate and physical activity. However, many techniques have been used in literature to predict blood glucose by considering recent CGM data as the single input [44–48]. In our study, we only focused on the literature that used machine learning models that used CGM as their single input. In the real-world other inputs such as physical activity, stress, meal intake, insulin injection are difficult to record continuously and automatically without the need of any human

Table 5 – Impact of additional time-domain features on the RMSE (mg/dL).

Model	Feature type		RMSE (mg/dL)			
	Last 30 min of BG	Time-domain features	15	30	45	60
SVR	√		13.13	17.86	22.68	27.08
	√	√	15.47	19.73	23.74	27.68
KNN	√		6.03	11.81	18.86	26.32
	√	√	7.89	12.65	18.66	25.25
DT	√		7.87	15.04	23.35	32.86
	√	√	7.82	15.33	22.33	32.26
RF	√		5.06	10.68	17.72	24.65
	√	√	4.86	9.85	16.38	23.21
AdaBoost	√		7.39	14.56	22.44	28.78
	√	√	7.44	13.56	20.24	26.76
XGBoost	√		5.42	10.79	17.20	23.49
	√	√	5.02	9.92	15.89	21.17
MLP	√		3.53	7.72	12.60	18.72
	√	√	2.82	6.31	10.65	15.33

Table 6 – Comparison with some other previous studies.

Study	Method	Subject	PH (min)	RMSE (mg/dL)
Perez-Gandia et al. [44]	ANN with last 20 min of BG.	15 T1D real patients	15	9.70
			30	17.50
			45	27.10
Wang et al. [45]	Adaptive-weighted-average framework based on AR, ELM and SVR	10 T1D real patients	15	±10
			30	±19
			45	±28
Hamdi et al. [47]	SVR based on DE algorithm.	12 T1D real patients	15	9.44
			30	10.78
			45	11.82
			60	12.95
Ben Ali et al. [46]	ANN with optimized input for each patient.	12 T1D real patients	15	6.43
			30	7.45
			45	8.13
			60	9.03
Martinsson et al. [48]	LSTM with 60 min of glucose level history.	6 T1D real patients	30	18.87
			60	31.40
Proposed model	ANN with additional time-domain features.	12 T1D real patients	15	2.82
			30	6.31
			45	10.65
			60	15.33

intervention. Therefore, obtaining accurate prediction output from prediction models with CGM as the single input is the goal of this work and would improve healthcare service by giving a flexible system for real diabetes patients to use.

We conducted a comparison with previous studies on BG prediction models with CGM as the single input and the results are presented in Table 6. Perez-Gandia et al. [44] used an ANN that used the last 20 min of blood glucose levels as input, while Wang et al. [45] utilized an adaptive-weighted-average framework based on AR, ELM and SVR. Ben Ali et al. [46] used customized feature input (i.e. a different feature size for each patient modelled) for ANN, while Hamdi et al. [47] used SVR combined with an GE algorithm to optimize the input parameters. Martinsson et al. [48] proposed a long short-term memory (LSTM) system to predict future blood glucose levels, given the last 60 min BG values as input. Finally, the experimental results showed that our proposed model outperformed the other methods except for the ANN proposed by Ben Ali et al. [46] for 45 min and 60 min PHs. Furthermore, for the 60 min PH the model by Hamdi et al. [47] showed better long-term forecasting compared to our model. Ben Ali et al. [46] used a "*recursive strategy*" for multi-step-ahead time series forecasting and it works by utilizing predicted one-step ahead values that are reused to produce the prediction for the next step, while in our study a "*direct strategy*" is utilized. This might explain why the ANN model by Ben Ali et al. [46] generated such good performance for long-term predictions (i.e. 45 and 60 min PHs) compared to our model. This conclusion is further supported by the experiment from Ben Taieb et al. [64] where a "*recursive strategy*" produced better performance results than a "*direct strategy*" on another dataset (i.e., NN5 competition datasets).

A direct comparison of the presented results is not fair since they have been derived by different dataset, preprocessing techniques and training/testing approaches. In addition, the performance of the prediction models depends on several factors, such as input features, hyperparameters, dataset type and its size, noise filtering method, etc. Therefore, this general comparison (Table 6) cannot be used as the main evidence to conclude the performance of a given prediction model but it can be used simply as a general comparison between the proposed model and previous studies.

5. Conclusion and future work

In this study, we proposed a prediction model based on a Multilayer Perceptron (MLP) for predicting blood glucose values multiple steps into the future. The direct and sliding window strategy was utilized to convert time series data into a set of paired inputs and desired outputs. This allowed conventional machine learning models to use this data as a training set and then generate prediction results. To improve the prediction results, time domain features (statistical features) were generated and combined with the last 30 min of BG values to be utilized as input features for the proposed MLP. The proposed MLP model showed the best performance by generating the lowest RMSE and MAPE but the highest R^2 compared to other prediction models. The RMSE of the predictions from the proposed MLP are 2.82, 6.31, 10.65 and 15.33 mg/dL for prediction horizons (PHs) of 15, 30, 45 and 60 min, respectively. Finally, by integrating the sliding window approach and time-domain features as attributes for the prediction models, we were able to reduce the prediction error compared to other prediction models using sliding window-based attributes only.

The dataset utilized in this study was limited to a small set of T1D patient (12 children), therefore it would be difficult to draw conclusions on the overall performance of the prediction models in this study in predicting future blood glucose (BG) levels. Other types of datasets such as those collected from other CGM sensors or glucose meters (SMBG) need to be utilized in the future. Furthermore, extending the comparison to other prediction models, optimizing the hyperparameters of the models and considering different strategies for multi-step forecasting could be presented in the near future.

Authorship statement

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

Declaration of conflict of interest

We confirm that all authors declare no conflicts of interest.

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