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Predicting Blood Glucose in Type-1 Diabetic Patients using Deep Learning Techniques - Approaches and Challenges

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ABSTRACT
Diabetes Mellitus (DM) is a metabolic disorder where the body fails to produce the digestive hormone insulin, or the body's ability to respond to insulin is limited. This situation leads to abnormal metabolism of carbohydrates and elevated blood sugar level. Type-1 diabetes (T1DM) is a condition arises mainly due to auto immunity disorder in which the immunity cells of the body mistakenly destroy the beta cells in the pancreas, which produce insulin. T1DM patients require to have proper control of their blood glucose level through proper medication, physical activities and continuous monitoring of blood glucose levels. A wide range of advanced wellbeing innovations, particularly computerized applications, have been growing quickly to assist individuals with dealing with their diabetes. Artificial Intelligence is a rapidly growing field, and its applications to diabetes research are becoming significantly more quickly. This paper is a review of six studies of existing neural network-based models for the prediction of future blood glucose level in T1DM patients and describes some challenges to predict future blood glucose with the available data. These models include prediction of blood glucose level using Convolutional Neural Networks (CNN), Feedforward Neural Network (FNN), Recurrent Neural Network (RNN) implemented using Long Short Term Memory (LSTM), Convolutional Recurrent Neural Network (CRNN), Bidirectional LSTM (BiLSTM) and Dilated Recurrent Neural Networks (DRNN)
Keywords: Diabetes Mellitus, Artificial Intelligence, Deep Learning, Convolutional Neural Networks, Feedforward Neural Network, Recurrent Neural Network, Long Short-Term Memory, Convolutional Recurrent Neural Network, Bidirectional LSTM, Dilated Recurrent Neural Networks

1. Introduction

Diabetes Mellitus is presently one of the life-threatening medical conditions around the world. At the point when we consumption carbs, our body transforms it into glucose which uninhibitedly streams in our circulatory system. It is the functionality of pancreas to discharges the digestive hormone, insulin, which will change over the surplus glucose into an alternate form called glycogen and store it in body cells and reuse it as per the energy needs of our body. In Typte-1 diabetic patients, the pancreas fails to produce insulin, which in turn affects the metabolism of carbohydrates. The excess glucose produced will flow freely through the circulatory system and it can damage all the vital organs of human body like kidney, eye, heart, nerves etc.

So, the T1DM patients completely depend on external artificial insulin to stabilize the level of glucose in blood. But the imbalance of external insulin, food intake and physical activities may either raise the blood sugar above the normal value or make the blood glucose level fall below the normal value. The former scenario is called hyperglycaemia and the latter one hypoglycaemia.

The new age brilliant medical care framework presented many trend setting innovations which assisted patients with overseeing their glucose level. To give appropriate insulin-based medicines to diabetic patients, constant glucose checking has been contrived utilizing Continuous Glucose Monitoring Systems (CGMS). A CGM ordinarily contains two sections, a sensor and a peruser/scanner. A minuscule sensor will be embedded under the patient's skin. The sensor estimates

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your glucose level, once in each 10-or 15 minutes. We can see the deliberate BG esteem through a screen. The screen could be an insulin siphon or a different gadget.
As with the growth of Artificial Intelligence (AI) a lot of studies are going on in the area of diabetes prediction. Already there are a huge number of studies about how to predict future blood glucose values in Type-1 diabetic patients. In this paper, we are presenting a review on six different works on blood glucose prediction in T1DM patients using deep learning techniques. The article is organized as; the section 2 describes the selected models, the methods used and analysis of each model, the third section provides the summary of the overall study. The fourth section describes the challenges in predicting blood glucose value using deep learning techniques and the fifth section concludes the paper.

2. Description of Models

This section describes the various models studied, and their topographies. All these models use different deep learning techniques to predict the future blood glucose in Type1 diabetic patients. They differ in the architecture used, the data set on which the study is conducted and the prediction horizon.

2.1 Taiyu Zhu, 2018

In [1], Taiyu Zhu developed a CNN based model for forecasting the future blood glucose level. It uses a modified version of WaveNet [2][3]. This model transfers the task into a classification problem, and is mainly built by casual dilated CNN layers and engages fast WaveNet algorithms. This method uses the glucose data of the patients are sequentially obtained by continuous glucose monitoring (CGM) in every five minutes. The variation of the current glucose value with the future glucose value is distributed to 256 target categories. Under such a context, the prediction problem is converted to a classification task, which can be solved appropriately. After pre-processing datasets and building the modified WaveNet model, the prediction results for 30-minute prediction horizons (PH) are obtained.

The dataset used here for training and testing are obtained from the OhioT1DM dataset developed by [Marling and Bunescu, 2018]. There are six patients with type 1 diabetes wearing Medtronic 530G insulin pumps and Medtronic Enlite CGM sensors to collect the data during the 8-week period [1]. This method uses the metrices such as previous glucose readings from the Continuous Glucose Monitor (CGM), and insulin value and carb intake recorded in the insulin pump.

The training data set is observed to be having missing fields in certain intervals. Since the accuracy of prediction by CNN rely on the difference between current and future data points, they used the method of first order interpolation to fill up the missing values. For the testing data, the first-order extrapolation is taken to ensure the future values are not involved. The predictions by extrapolated intervals are cancelled to make sure that the result is similar to the CGM testing data in the measure of data length, when evaluating the performance. In this model, the data points with large missing gaps are discarded, and the values only for short intervals are interpolated. A part of the data with the longest continuous interval from other subjects are combined into the current subject to form an extended training data. After interpolation and combining, there are many small hikes near the peak or turning values. They have used the technique of median filtering to clear this noise or variance from the data set.

After pre-processing of training data, the WaveNet system is constructed which focuses on the long-term relationships between channels and is conditioned on all previous samples. The key machineries in WaveNet are causal convolutional layers. After shifting the outputs by several data points, the 1- D causal convolution layers can be implemented. The main ingredient is causal dilated convolutional neural network (DCNN) layer, which involves a larger number of input nodes. Hence the system becomes capable of learning long-term dependencies by avoiding certain steps that determined by the dilation factor.

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There are four channels in the inputs of the neural network: CGM data, insulin event, carbohydrate intake, and time index. The sets of the testing phase have the similar organization. The PH is 30 minutes, so it is required to estimate the CGM values 6 points in the prediction. Therefore, the difference in glucose value between the present value and the future value in the PH. The method of quantisation put the change of glucose values in 256 classes as goals with a difference of 1 mg=dl between each class.

When focused on the RMSE for each patient and recorded the results of several rounds, the average best result of Root Mean Square Error for this method was 21.7267 with a standard deviation of 2.5237. When we analyse the final results, it was observed that the prediction error is high during the insulin and meal events. Also, near the data points of missing values, the error was observed to be high since the predictive curve is calculated based on the previous values.

We can not directly compare the RMSE values observed in this method with other technologies since the data sets are collected from different subjects. The overall working of this method is summarised in Figure1.

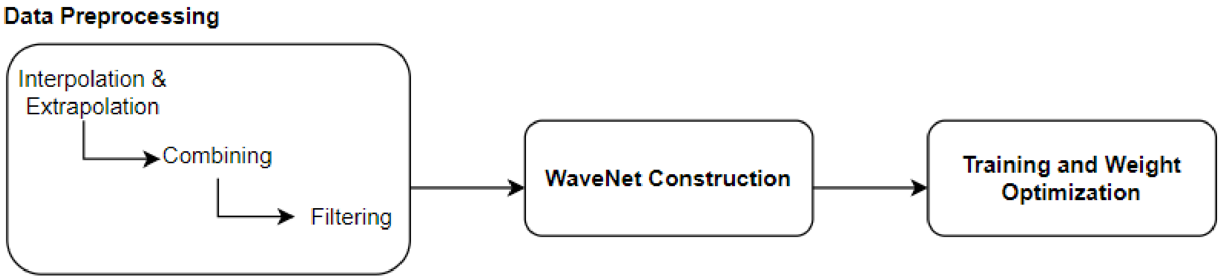

Fig1: Block Diagram of Taiyu Zhu, 2018

2.2 Muhammad Asad, 2019

This paper [4], they have investigated virtual CGM data of 10 subjects taken from AIDA directory to predict the future diabetic concentration using Feed Forward Neural Networks (FNN). Here, the previous blood glucose values are only taken under consideration for the prediction of future values. The dataset used in this paper was taken from a free online mathematical diabetic simulator called AIDA. It has 40 case studies with different age group, diseases, and meal intake. Each data set consists of 24 hours of data for a particular subject. The sample size is 15 minutes. Among these, only 10 case studies are used in this paper.

FNN has three layers, input layer, hidden layer and the output layer. The number of input values are taken proportional to the number of input neurons. The hidden layer is responsible for weight assignment. Here the tangent sigmoid transfer function is used. The training algorithm Levenberg-Marquardt [6].is used to randomly initialize and update weights and biases for speedy convergence. Firstly, the data is normalized, variables are initialized, then train the neural network and finally RMSE is calculated for each iteration. This method works in a prediction horizon (PH) of 15 minutes. The data has been split into 70% for learning and 30% for testing.

The performance here is measured using the RMSE value. The analysis after training in this method shows that the average RMSE was observed to be 1.26 ml/dl. When compared with the previously available studies, this method was observed to have the best prediction value. Table 1 summarises the architecture constraints of this model.

Table 1: Muhammad Asad's Model architecture parameters

Type	FNN
Input Layer Neurons	15
Hidden Layer Neurons	15

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Output Layer Neurons	1
Training Algorithm	Levenberg-Marquardt
PH	15 mins

2.3 Fayrouz Allam, 2011

Article [8] is a deep learning-based model using Recurrent Neural Networks (RNN) which aims to predict the future blood glucose concentration for a PH of 15, 30, 45 and 60 minutes. The data set for this model has been collected from nine Type 1 diabetic patients with an average duration of glucose measurements for 2 days, 288 samples per day. The data was smoothed using low pass filter of order 11 before using it in training and testing the neural networks, so that the time lag between the measured value and the predicted value can be reduced.

The model uses an RNN predictor, the input to which is the glucose readings of sample I and output yi is the predicted glucose reading at time i+PH. The performance of this model is accessed using the RMSE in mmol/L. From the results, it can be observed that for longer PH values there is no much difference between the proposed model and other prediction models. But for shorter PH, the prediction model using RNN 20-13-1 architecture gives the best result. Table 2 shows the RMSE and Normalized Prediction Error (NPE) when using 40 inputs and (20-13-1) for different PHs

Table 2: RMSE and NPE when using 40 inputs and (20-13-1) for different PHs

PH	RMSE (mmol/L)	NPE (%)
15	0.14	1.7
30	0.42	5.27
45	0.84	10.28
60	1.32	16.2

[8]

2.4 Kezhi Li, 2019

This model [9] presents a deep learning model to accomplish forecasting glucose levels with high accuracy for simulated patient cases using Convolutional Recurrent Neural Networks (CRNN). This approach is evaluated on a dataset of 10 simulated cases generated from the UVa/Padova simulator and a clinical dataset of 10 real cases each containing glucose readings, insulin bolus, and carbohydrate data. [9]

In this model prediction is done using a multi-layer convolutional recurrent neural network (CRNN) architecture. The architecture of the CRNN has three parts: a multilayer convolutional neural network that extracts the data features using convolution and pooling, followed by a recurrent neural network (RNN) layer with long short term memory (LSTM) cells and fully-connected layers.

The data used in this model includes both clinical as well as those taken from UVA/Padova T1D. CGM data recorded every 5 minutes, meal data indicating meal time and amount of carbohydrates, as well as insulin data with each bolus quantity and the associated time are given as input to the CRNN. The clinical data usually may contain missing data or outlier data due to errors in calibration and measurements. So, it is necessary to purify the input data. So, in the pre-processing stage, the use the Gaussian filter is used to smoothen the clinical data.

The result of pre-processing is cleaned as time-adjusted glycaemic, carbohydrates and insulin information, and then they are passed to the CNN. The output of CNN fills in as the contribution of RNN, which is a multi-dimensional time series information, addressing the connection of elements of the original signals. The result of the RNN is the prescient BG level 30-min (or 60-min) later, while hidden states are acquired and refreshed ceaselessly inside within the RNN part. The model is prepared start to finish.

A LSTM network involved 64 LSTM cells is embraced as recurrent layers. The output of the CNN, a multi-dimensional time series, is associated with the LSTM organization. We created a RNN with

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1 hidden layer, comprising of a wide LSTM layer comprising of 64 cells. the proposed model has a transform and a recuperation step. They adjust BG esteems previously, then after the fact the regular LSTM. the last layer of RNN takes care of a multi-facet completely associated network, which comprises of 2 hidden layers (256 neurons and 32 neurons) and an output layer (a single neuron) with the glucose change as result. The RMSE for the predicted results for different PH is shown in Table 3.

Table 3: RMSE values for PH 30 and 60

PH	RMSE (for 10 virtual data)	RMSE (for 10 real clinical data)
30	9.38 mg/L	21.07 mg/L
60	18.37 mg/L	33.27 mg/L

2.5 Taiyu Zhu1, 2020

The paper [12] describes a profound learning model dependent on a dilated recurrent neural network (DRNN) to give 30-min estimates of future glucose levels. Utilizing enlargement, the DRNN model acquires a lot bigger receptive field in terms of neurons targeting catching long haul conditions. A transfer-learning procedure is likewise applied to make utilization of the information from multiple subjects.

The engineering of the DRNN model mostly includes a series of DRNN layers with various sizes of dilation. Each DRNN layer comprises of the recurrent neural network (RNN) unit with a lot of hidden nodes, which can be long short term memory (LSTM), gated recurrent units (GRU) or simple vanilla cells.

Two sets of data are used in this model to evaluate the performance of the DRNN models: OhioT1DM from clinical trials and in silicon dataset from the UVA-Padova simulator. The clinical data are pre-processed using the methods interpolation or extrapolation, filtering and combination to cover up the missing values before training the model. Here, first train a summed-up model on this joined dataset. Then, at that point, a subsequent stage preparing is directed dependent on the prepared model and individual information for a particular T1DM subject by utilizing a transfer learning approach. Exploratory outcomes show that this two-stage strategy builds the size of preparing dataset and the consensus of the model, and it gets a superior forecast precision practically speaking.

In the case of dilated RNNs, certain numbers of timesteps are hopped from the result of the previous stage, in each hierarchical layers. Unlike fully connected RNNs, the DRNN uses less parameters which augments the proficiency of training and lighten the gradient vanishing problem. Also, DRNN allows parallel processing which is apt for GPU computation. With this parallel implementation, this model further reduces training time.

In this model, the mini-batch approach is used with a subset of the data to update parameters for each training step. During the training, the hyper parameters are tuned manually. The combinatorial space is not very large, so grid search for each hyperparameter is performed. Extracted 10% data from the end of training datasets as the validation datasets and kept the first 90% data to train the models. Hence, for the simulated dataset, the overall split is 81% for training, 9% for validation and 10% for testing.

When DRNN is fed with the historical data, and length of sequences was tuned among {6, 12, 18}, it was observed that the model showed minimum RMSE value with length=12. For the simulated T1DM subjects, this model showed RMSE of 7.8 mg/dl with a standard deviation of 0.6. For clinical data, this model has an average RMSE value of 18.9 mg/dl with a standard deviation of 2.6.

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2.6 Qingnan Sun, 2018

The prediction model uses a sequential model with one long-short-term memory (LSTM) layer, one bidirectional LSTM layer and several fully connected layers was used to predict blood glucose levels for different prediction horizons [11]. In this model, only blood glucose data taken from CGM are considered to predict the future glucose values.

LSTM is a variant of RNN network. Bidirectional RNN (BRNN) can be prepared utilizing all accessible info data in the past and fate of a particular time. By parting the state neurons of a customary RNN into the positive and negative time headings, the organization disengages the yields from forward states and in reverse states. During the preparing process, BRNN is prepared in both forward and in reverse ways. Bidirectional construction can be applied to the variations of the RNNs; in this work we utilized bidirectional LSTM.

This model uses one LSTM layer and one bidirectional LSTM layer, each with 4 units, and three completely associated layers with 8, 64 and 8 units, individually. The yield layer, the one-unit thick layer, was utilized to yield the last anticipated blood glucose esteem. It has two rounds of pre-train with both simulated and real patient data. Table 4 shows the RMSE values of prediction results of this model corresponding to different PH values.

Table 4: prediction results of Qingnan Sun

PH	RMSE
15	11.633
30	21.747
45	30.215
60	36.918

3. Summary

This article reviewed six different studies on blood glucose prediction using different deep learning algorithms. These models differ in the deep learning model used, the training data set and the metrices used to assess these models. In this paper, we have used the metric RMSE derived by each of these models to compare their performance. But simply by a minimum value of RMSE, we cannot insist that model to be the best prediction method. Some of these models were evaluated on realistic data, and some on simulated data. In the case of real clinical data, there can be discontinuities in the sequence of input data due to missing values in some time intervals. Also, the real clinical data may contain noise, whereas the simulated data will be sequential and smooth. The review on the selected articles is summarised in Table 5.

Table 5: Summary of review on selected papers

Ref #	Model	Data Sources	Development Process	Metric used for Analysis	RMSE
[1]	Casual dilated CNN	OhioT1DM	Interpolation & extrapolation, Combining, Filtering using median filter, Training (Making Batches and weight optimization	RMSE	21.7267 ± 2.5237 mg/dL
[4]	FNN	AIDA Simulator	normalize the data, initialize the variables, train ANN	RMSE	1.25 ml/dL

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			and calculate the root mean square error is at each iteration.		
[8]	RNN	clinical data of Type 1 diabetic patients	smoothening using low pass filtering, training RNN	RMSE FIT NPE	PH 15: 0.14 PH 30: 0.42 PH 45: 0.84 PH 60: 1.32
[9]	CRNN	clinical data of Type 1 diabetic patients, UVA/Padova T1D	Outlier Detection and Filtering, Construction of multi layer CNN, Modified Recurrent laryer	RMSE MARD	PH 30: 9.38 ± 0.71 PH 60: 18.87 ± 2.25
[12]	DRNN	OhioT1DM from clinical trials and in silicon dataset from the UVA-Padova	Data acquisition and Pre-processing, recurrent layers, multi-layer dilated connections, Network training, Hyper parameter tuning	RMSE MARD	Simulated data : 7.8 ± 0.6 For clinical data: 18.6
[11]	BiLSTM	real patients datasets and *in silico* datasets of UVa/Padova T1D		RMSE, [mg/dl], correlation coefficient (CC), time lag (TL, [min]), FIT	PH 15: 11.633 PH 30: 21.747 PH 45: 30.215 PH 60: 36.918

4. Challenges

The main challenges involved in predicting the future blood glucose value of a Type-1 diabetic patient using deep learning techniques involves the following characteristics.

4.1. Types of inputs and availability

There are a lot of physical as well as situational characteristics that affect the blood glucose level of a patient. Some of these factors are assessable and some are not. While predicting the future blood glucose value, the main factors to be considered are current blood glucose value, insulin intake, carbs intake and physical activities carried out by the patient in terms of carbs burned. There are the major aspects that could determine the upcoming blood glucose value. We can measure the previous blood glucose values from a continuous glucose monitor. The amount of insulin intake can be collected from insulin pump. The total carbohydrates intake is difficult to get because it is to be manually calculated by the patient or a health care professional. Even if there are equipment like smart watches and bands which can measure the amount of carbs burned, we cannot completely depend on the data collected from such devices.

The relationship between two intermittent blood glucose readings is an effect of the former reading, food intake during the interval or within two hours before the latter reading, physical activity during that time and insulin intake that covers the time of the latter reading. But there is no such mechanism to simultaneously measure these values. The amount of carbs burned and carb intake is not accurately measurable. Even if it is possible, the insulin correction value may vary from person to person. This may inversely affect the prediction

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4.2 External factors that affects blood glucose level

Type-1 diabetes usually occurs at young ages and it happens due to autoimmunity. In the case of Type-1 diabetic patients, there are a lot of other physical as well as emotional aspects that may affect the blood glucose level. They are hormonal imbalances, other deceases caused by diabetes itself, other medications, stress and even sleep deprivation and mood changes may cause the blood glucose level to either rise or fall beyond the normal level. The common characteristics of all these are they are not directly quantifiable.

Even if we use the main four factors mentioned in the studies mentioned, the result may slightly vary from realness. A wrongly predicted blood glucose level may lead to inappropriate food intake or medication.

4.3 Choosing the Proper Methodology

There are a lot of studies carried out already for predicting blood glucose level using various ML Techniques. Most of these methods used the previous blood glucose level to predict the future value. Only very few of these methods used real clinical data. Some of these works used simulated data. Even if it showed better accuracy in prediction, we cannot trust such models with real data. Because the simulated data will be perfect, without any missing data or noises, unlike real clinical observations.

A wide variety of Machine Learning Algorithms are there for predicting the future blood glucose level. There are a number of factors that determines which algorithm to be used for blood glucose prediction like the types of input data used for training the model, the quantity of features, and the amount of collected data. Most of the previous studies used the autolearning capability of Artificial Neural Networks. These models have been evaluated using different performance metrices like RMSE, Accuracy, Sensitivity and Specificity. So, it is difficult to perform a quantitative comparison of the algorithms.

4.4 Prediction Horizon

Prediction horizon can be defined as the time how far with which the model predicts the future. Almost all of the previously conducted studies based on ML models predicted the future blood glucose values within a PH of 15 to 60 minutes. The main purpose of predicting future blood glucose is that, the patient or health care professionals could take necessary measures to prevent events such as hypoglycemia or hyperglycemia. A time interval of 15 or 30 minutes is not seemed to be sufficient for taking necessary health care strategies to prevent the critical events.

Various studies shows that higher PH values leads to higher rate of errors. When a new model is constructed, there should be a balance between the time a patient needs to respond, and the error related to estimation while choosing the PH value.

CONCLUSION

DM is one of the most life-threatening conditions nowadays. With the evolution of AI, a lot of studies are ongoing to predict and analyse blood glucose concentration in diabetic patients. In this paper, we have done a review of six different models for the prediction of future blood glucose level in T1DM using deep learning techniques. Each of these models works on different deep learning models, and are analysed under different scenarios. Here we have described the prediction accuracy of each of this model using their RMSE value derived in the respective studies. As per the review, the model [8] which uses RNN for prediction, is having minimum value of RNN with respect to different prediction horizon. The accuracy of prediction of these models cannot be directly compared, since they are implemented in different scenarios using different data sets.

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