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A Multi-Network Fusion Prediction Method for Patient Blood Glucose Concentration Prediction and Hyper/Hypoglycemia Blood Glucose Warning

Yanran Wang [1], Wenping Liu [1] and Haoyu Jin [1+]

[1] Institute of Medical Devices, Guangdong Food and Drug Vocational College, Guangzhou, Guangdong, China

Abstract. To cope with the inconvenience as well as potential dangers of glycemic management in diabetic patients, we propose a fully automatic blood glucose prediction method based on neural networks. This method adopts a voting strategy to merge the advantages of regression prediction and classification prediction to construct a multi-network fusion prediction model, which can achieve the following dual objectives: (1) hyperglycemia and hypoglycemia warning with a time interval of 30 minutes, while the warning results have high reliability; (2) real-time blood glucose concentration prediction. To verify the effectiveness of our method, we tested 19 simulated patients in UVA/Padova T1DMS. The results show that our method can achieve the objectives well, and it also has better performance than the commonly used single neural network method.

Keywords: diabetes, neural network, blood glucose, prediction algorithms

1. Introduction

Diabetes has become the third major disease affecting human health which bring heavy burden to the development of society. Many medical devices have been developed for the management of diabetes, especially Continuous Glucose Monitoring (CGM) sensors that measure Blood Glucose (BG) levels over several days or weeks at intervals of 1~5 minutes [1]. Since then, the treatment of diabetes is mainly through the patient's self-monitoring of BG 3-4 times a day for diet, physical exercise, insulin, and other medication replenishment. However, this method of BG management is not ideal, and the BG concentration often exceeds the normal range (70~180 mg/ dL) due to the lack of timely BG monitoring, resulting in hyperglycemia or hypoglycemia. Therefore, it is still a challenge of great significance to predict future BG concentration levels in advance and give patients sufficient time for prevention and treatment, which can reduce their frequency and duration or even avoid hypoglycemia and hyperglycemia.

Many researchers have been developing hypoglycemic and hyperglycemic prediction models using statistical and machine learning methods. In 1999, Bremer and Gough [2] first attempted to use past BG values to predict future BG levels. The hypoglycemia prediction method proposed by Zecchin et al. [3] used 50 virtual patients in the UVA/PADOVA simulator to simulate and compare the duration of hypoglycemia in three situations: no hypoglycemia was detected by any device; patients had a snack intervention when they exceeded the hypoglycemia threshold; and a 30-minutes predictive warning of hypoglycemia onset. Experiments showed that predicting the occurrence of hypoglycemia and hyperglycemia in advance can effectively reduce the duration of abnormal BG and maintain the normal BG level of patients.

In addition, Plis et al. [4] proposed a machine learning method for predicting BG levels and the occurrence of hypoglycemia. They used a support vector regression method to accurately predict 23% of hypoglycemic events at a prediction interval of 30 minutes. Agrawal et al. [5] proposed a strongly supervised machine learning approach to determine the probability of occurrence of hyperglycemia and the effect of physical activity, such as exercise. Bertachi et al. [6] used multilayer perceptrons and support vector machines to generate personalized prediction models that could predict over 70% of nocturnal hypoglycemia.

[+] Corresponding author. Tel.: +86-020-29164611; fax: +86-020-29164611.
E-mail address: jinhy_gdyzy@163.com.

Zhu et al. [7] processed BG measurements from CGM sensors for real-time prediction of BG by building a long and short-term memory recurrent neural network. In addition, many researchers have explored studies on BG prediction using only historical CGM data, starting from regression models, artificial neural networks, and kernel-based methods [8-10]. Other scholars considered that the BG level is affected by the amount of carbohydrate intake, insulin injection and various physical activities, and proposed to use some or all of these influencing factors to predict BG level [11-12].

Although there have been many attempts on BG prediction, and many research works have proved that neural networks have good effect in solving the BG prediction problem. However, most existing BG prediction methods used historical BG data combined with other physiological, dietary and exercise data to make future BG prediction, which requires manual intervention and is not fully automated reasoning for BG prediction. In addition, the accuracy of existing neural network-based BG prediction methods needs to be improved. Therefor, we propose a multi-network fusion method for BG prediction. Our contributions are:

(1) Achieved the dual goals of automatic hyperglycemia and hypoglycemia warning and BG concentration prediction, with prediction intervals of 30 minutes.

(2) Proposed a fusion strategy, which fuses regression network and classification network to improve the accuracy and reliability of prediction results.

2. Proposed Approach

In order to cope with the diabetes challenges such as the generation of various complications and the living inconvenience, we propose to establish a closed-loop intelligent monitoring system for BG without manual intervention, which can predict future BG fluctuations based on the continuous monitoring data of human real-time BG, as shown in Fig. 1. On the one hand, it can provide early warning of upcoming BG abnormalities, such as hyperglycemia or hypoglycemia. On the other hand, it can also provide a basis for immediate, micro, and dynamic adjustment of insulin pump dosing, greatly reducing the fluctuation range of patients' BG and controlling the BG level in the normal target range. In order to achieve this closed-loop system, the foremost thing is to accurately predict the patient's future BG during a given period of time.

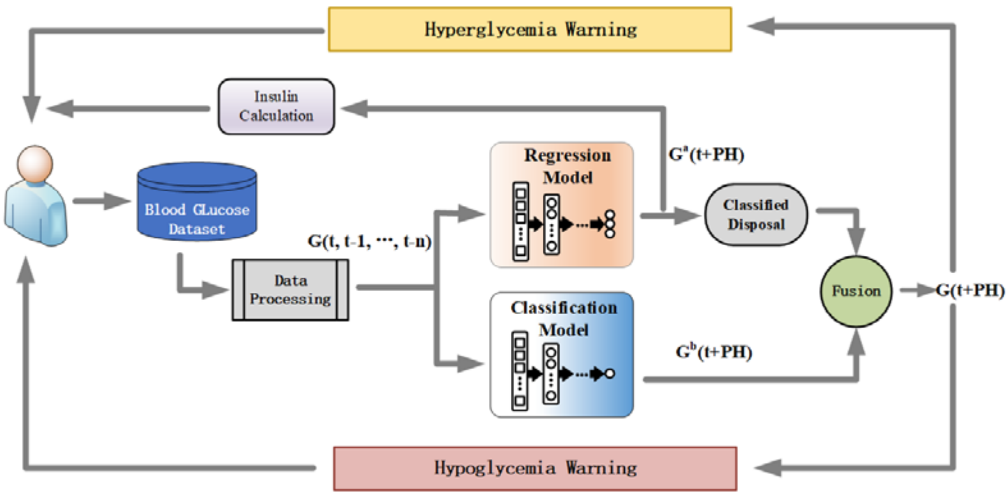


Fig. 1: Closed-loop intelligent BG monitoring system without manual intervention.

2.1. Neural Network Predictive Model

Glucose metabolism in diabetic patients is complicated. It is difficult to obtain a reliable, accurate mathematical model of BG concentration prediction. However, neural network technology is particularly suitable for solving such complex nonlinear prediction problems. Therefore, we established regression prediction model and classification prediction model based on neural network to solve the problem of BG prediction in this paper.

We construct two network prediction models with the same structure. The network structure is shown in Fig. 2, which is a fully connected four-layer neural network structure consisting of interconnected nonlinear units with adjustable weights. The connections can be expressed in the following form.

$$\chi_l^i = \delta_l^i (w_l^i \chi_{l-1} + b_l^i) \tag{1}$$

Where χ_l^i is the output value of the $i-th$ neuron in the $l-th$ layer. δ denotes the *tansig* activation function, defined as $\delta(z)=\frac{2}{1+e^{-2z}}-1$. w is the weight parameter, b is the error value. w and b can be given initial values during model initialization and optimized through network model training.

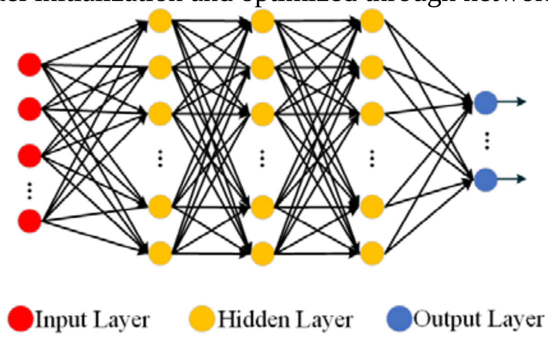


Fig. 2: Network connection structure of the prediction model.

The network prediction models constructed in this paper are set with initial learning rate of 0.05, target error of 0.00001, and 10,000 iterations. The networks are all optimally trained using the gradient descent method. Where the regression prediction model is constructed with six inputs, one output, and the number of hidden layer neurons is $[20,15,10]$. The mean square error is used as the loss function, expressed as:

$$\Gamma_A=\frac{1}{m}\sum_{i=1}^{m}(\overline{\chi}_i-\chi_i)^2 \tag{2}$$

The classification prediction model is constructed with six inputs, three outputs, It has the same number of hidden layers as the regression prediction model. The cross-entropy loss function is used to calculate the gradients, expressed as:

$$\Gamma_B=-\frac{1}{m}\sum_{i=1}^{m}\sum_{j=1}^{n}\chi_j\log\overline{\chi}_j \tag{3}$$

2.2. Model Fusion Strategy

Most of the existing literature based on neural network techniques use only one type of model to solve the glucose prediction problem, such as the regression-based prediction models or the classification-based prediction models. These methods do have performance in solving the BG prediction problem. However, for the single regression model, we found through many experiments that no matter how good the model is, the real-time tracking prediction of BG tend to fluctuate greatly at the inflection point where the BG curve changes fastest, resulting in poor prediction of hyperglycemia or hypoglycemia. The single classification prediction model is also prone to false-negative or false-positive errors, which is very dangerous for the diagnosis of diseases.

Considering the advantages and disadvantages of single regression network and classification network model, we propose a multi-network fusion method to improve the accuracy of neural network in predicting abnormal BG. At the same time, real-time prediction of BG concentration is also achieved to provide a basis for patient treatment. The multi-network models are fused for prediction using the following steps.

Step 1: Unified neural network regression prediction and classification prediction results. The neural network prediction results are divided into two categories:

When the predicted BG concentration is $g<70\,mg/dl$, it is defined as hypoglycemia, and the predicted BG results at that moment is divided into category 0.

When the predicted BG concentration is $g>180\,mg/dl$, it is defined as hyperglycemia, and the predicted BG results at that moment is divided into category 1.

Step 2: Joint voting to predict hyper-/hypoglycemic outcomes.

At time t, if $\zeta_A^t=\zeta_B^t$, the joint result of the dual network model $\zeta^t=\zeta^t{}_A$ or $\zeta^t=\zeta^t{}_B$.

if $\zeta_A^t\neq\zeta_B^t$, the joint result of the dual network model $\zeta^t=\min(\min(|\zeta^{t-1}-\zeta_A^t|),|\zeta^{t-1}-\zeta_B^t|)+\zeta^{t-1},1)$.

where $\zeta^t{}_A$ is the regression prediction results and $\zeta^t{}_B$ is the classification prediction results.

3. Experiments

3.1. Experimental Software and Dataset

We completed the building and testing of our model in MATLAB. Data were obtained from UVA/Padova T1DMS, a diabetes simulation treatment test software approved by FDA to replace animal experiments, which included 10 virtual adult diabetic patients and 10 adolescent diabetic patients [13]. Among them, adult 09 was excluded because endogenous glucose production is suppressed even 6 hours after a meal, resulting in hypoglycemia [14]. The meal regimen is proposed to four meals a day, including breakfast, lunch, dinner, and snacks. The maximum single meal was 75g and the minimum was 20g. The daily meals fluctuated. We continuously monitored and recorded patients' real-time BG data for 30 days. Then we divided the data set into the first 23 days and the last 7 days for training set and testing set respectively to evaluate the performance of the network model.

3.2. Hyperglycemia and Hypoglycemia Warning

The warning accuracy of the proposed network for hyperglycemia and hypoglycemia in 9 adult patients and 10 adolescent patients is shown in Table 1. In terms of hypoglycemia warning, the accuracy was higher than 78% in all 18 patients, with a mean prediction accuracy of 84.2%, except for Adolescent 05 patients who had poor performance due to their large fluctuation span at the hypoglycemia threshold of 70 mg/dl. As for hyperglycemia, the accuracy of most patients was higher than 78%, and the average prediction accuracy was 87.18%. However, Adult 02, Adult 10 and Adolescent 06 had fewer occurrences of hyperglycemia, which was different from other individuals in the group, leading to errors in the prediction results of both the regression model and the classification model. So it shows a low warning accuracy of the fusion network.

Table 1: Performance of the proposed method for warning hyperglycemia and hypoglycemia in 19 patients

Subject	Warning Accuracy (%)		Subject	Warning Accuracy (%)	
	Hypoglycemia	Hyperglycemia		Hypoglycemia	Hyperglycemia
Adult 01	79.83	82.28	Adolescent 01	91.06	98.62
Adult 02	83.74	63.83	Adolescent 02	80.11	97.79
Adult 03	100	89.47	Adolescent 03	96.64	94.29
Adult 04	95.12	95.56	Adolescent 04	85.42	98.62
Adult 05	78.14	81.44	Adolescent 05	40.00	95.31
Adult 06	100	99.64	Adolescent 06	94.52	66.67
Adult 07	100	99.71	Adolescent 07	94.84	97.64
Adult 08	95.67	82.67	Adolescent 08	100	98.57
Adult 10	100	38.78	Adolescent 09	100	96.96
			Adolescent 10	79.46	78.61

Table 2 demonstrates the accuracy comparison between the proposed multi-network fusion model and the single regression and classification network model in warning hyperglycemia and hypoglycemia. From the experimental results, it can be seen that the proposed multi-network fusion model, and the fusion strategy are effective and improve the accuracy of neural networks in hyperglycemia and hypoglycemia prediction.

Table 2: Comparison of the proposed method and other methods in warning hyperglycemia and hypoglycemia

Subject	Methods	warning Accuracy (%)	
		Hypoglycemia	Hyperglycemia
Average Adult	Regression Model A	83.21	76.53
	Classification Model B	72.48	79.86
	Proposed Fusion Network A+B	**86.50**	**81.49**
Average Adolescent	Regression Model A	81.90	89.00
	Classification Model B	81.69	91.50
	Proposed Fusion Network A+B	**82.76**	**92.31**

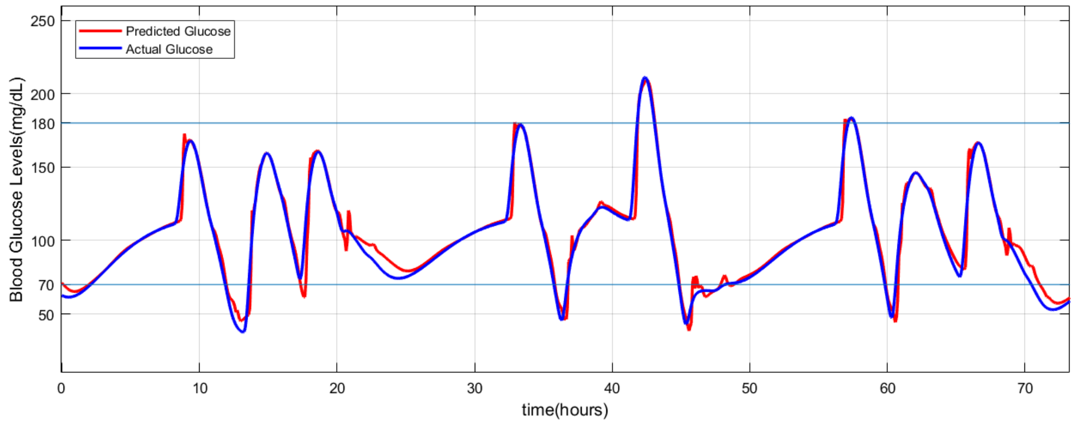
3.3. BG Concentration Prediction

To demonstrate the effectiveness of our method in predicting BG concentration, we report the RMSE performance of the proposed method in each individual patient in Table 3. Compared with adults, there are more influencing factors and more changes in the BG of adolescents, so it shows a slightly worse prediction result for the adolescent patient group than the adult patient group.

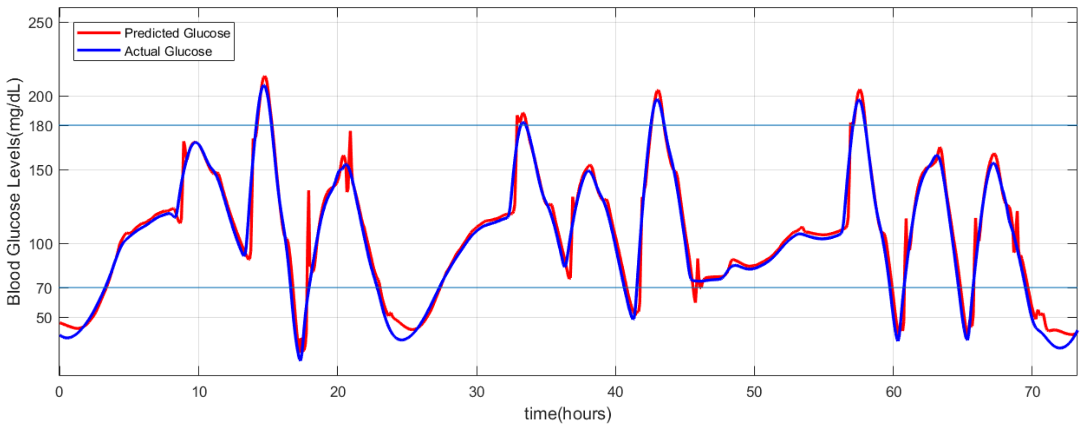
Table 3: Comparison of the proposed method and other methods in predicting hyperglycemia and hypoglycemia

Subject	RMSE（mg/dl）	Subject	RMSE（mg/dl）
Adult 01	9.00	Adolescent 01	15.82
Adult 02	9.11	Adolescent 02	18.11
Adult 03	6.97	Adolescent 03	7.78
Adult 04	6.74	Adolescent 04	9.26
Adult 05	7.91	Adolescent 05	11.07
Adult 06	8.63	Adolescent 06	11.18
Adult 07	7.02	Adolescent 07	14.32
Adult 08	7.20	Adolescent 08	9.87
Adult 10	7.35	Adolescent 09	10.54
		Adolescent 10	16.13
Average	7.77	Average	11.99

Meanwhile, taking Adult 04 and Adolescent 01 as examples, we show the qualitative comparison results between the predicted BG values and the real BG values in Fig. 3. From the BG concentration curves in the figure, it can be seen that, except for slight fluctuations at the inflection point of the curve, the perfect tracking prediction of BG can be achieved in most cases.



(a) Adult 04



(b) Adolescent 01

Fig. 3: The qualitative comparison between the BG values predicted by our method and the real BG values.

4. Conclusion

In this paper, we propose a new multi-network fusion prediction method for diabetic glucose prediction. The method is based on a neural network model and uses a fusion strategy to combine the advantages of regression prediction and classification prediction, thus achieving the dual objectives of BG prediction and high and low BG warning with a time interval of 30 minutes. The experimental results prove that the method is effective in BG prediction problem and improves the accuracy and reliability of neural networks in hyperglycemia and hypoglycemia warning.

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