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Effects of external factors in CGM sensor glucose concentration prediction

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Abstract

It is naturally desirable to avoid hypo/hyperglycemic events andcommercial devices exist that can alert the patient before they occur. It is known, however, that percentage of false alerts for those devices is still high and much is still needed to be done to improve that.

The purpose of this paper is to design a blood glucose prediction system that can be used aspart of a continuous glucose monitoring (CGM) device. With the help of a Kalman filter, glucose concentration is first reducedof its random noise component, and a neural network is then used for prediction of glucose upto two hours. Finally, this system is thoroughly tested for accuracy against various externalfactors. It is shown that such factors as patient's body weight, his/her exercise period andlifestyle may influence how well glucose concentration is predicted and therefore should betaken into account for early and accurate detection of hypo/hyperglycemic episodes.

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Keywords: Diabetes; CGM; Kalman Filter; Neural Network; Glucose Concentration.

1. Introduction

Diabetes mellitus isa metabolic disease that has been affecting the lives of many in recent years. In order to help improve the lives of millions of diabetic patients,continuous glucose monitoring (CGM) is a choice that is often used to monitor any wrong activity contributed in glucose trend variations.

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There have been many research activities in recent years on the use of CGM in tackling diabetes. An inclusive search has been done by the Direct Net study group[1], which analyzed the enhancement in CGMsensors accuracy by looking back and modifying the number and timing of the calibration points. The results of this study lead to the conclusion that the timing of the calibration points is even more imperative than its number. Marchetti et al.[2] suggested an improved proportional integral derivative (PID) control approach for blood glucose management.Stemmann et al.[3], considered that a calibration model could be obtained involving original blood glucose data and noise added to the measurements of the non-invasive glucose monitoring (NIGM) sensor. Using this procedure, the impact of the original data and the noise on the sensor data could be analyzed.

Kalman filter (KF) was used for the first time to process CGM information in the work of Knobbeand Bukingham[4]. Most favorableestimation with the aid of KF has been done by Palerm etal.[5], where they aimed topredict the glucose trend in detecting hypoglycemia. Kuure-Kinsy et al.[6] employeda dualrateKF for real time CGM in order to improve itscalibration. The topic of denoising CGM has been more extensively tackled by Facchinetti etal.[7], who have proposed a method based on a Bayesian estimation by a KF. They[8] also suggested a new online approach to denoise CGM signals using a KF, whose unknown parameters are tuned to an individual.

Savage et al.[9] formed an artificial neural network (ANN) to figure out the CGM sensoroutput plus the system parameters, and showed a relationship between them and blood glucoselevels. A supervised back propagationneural (BPN) network was used for obtaining blood glucose in diabetic patients by Ashok et al.[10]. Pappada et al.[11] utilized NeuroSolutions software to make different neuralnetwork (NN) models with variable predictive windows.

Facchinetti et al.[12] introduced again a new technique for noise reduction that is able to deal alsowith the intraindividual varying of the signal to noise ratio(SNR).Shanthi and Kumar[13] studied in their research the removal of errors caused bydifferent noise distributions in CGM sensor data. A feed forward NN and Extended Kalman Filter (EKF) algorithm were used to reduce the effects of various noise distributions in CGM time series. Zecchin et al.[14] aimed in their work to build up a new short-term glucose prediction systembased on a NN.

Panteleon and colleagues[15] improved the calibration of CGM with aid of a seventh orderFIR filter. Keenan and associates[16]studied thedelays in two different CGM devices, by a demonstration analysis of the data set todetermine a modern calibration algorithm utilized in the Paradigm Veo insulin pump.An integral based fitting and filtering algorithm for a CGM signal wasdeveloped by Chase et al.[17].

In this study, the goal is to investigate the effects of external factors such as body weight, exercising and lifestyle of a patient in CGM blood glucose prediction. To accomplish this, first, noise associated with the CGM device is removed using a KF. Then, a backpropagation NNis used to implement a prediction system for the filtered glucoseconcentration.

2. Glucose concentration prediction system

The aim of this paper is to design a system for glucose concentration prediction of diabetic patients and analyze the performance of it against different factors. Data is taken from GlucoSim software[18], which simulates a continuous glucose monitoring (CGM) system, and is fed to a network comprising of a KF and an ANN (Fig. 1). In this approach, KF is used to denoise the CGM sensor data, and ANN model acts as a predictor. Using the back propagation algorithm and two predictive windows, NN predicts glucose values up to two hours. This helps avoid hypo/hyperglycemia, which can lead to serious complications.

3. Denoising of CGM sensor data using a Kalman filter

It must be noted that the accuracy of CGM data may be affected by different error sources. In particular, defective calibration and random noise component can corrupt the CGM signal. This paper deals with the reduction of this component. To improve the signal quality andreduce this error, digital filtering techniques are used. In more strict terms, if following equation is considered,

$$y(t) = x(t) + n(t) \quad (1)$$

where $y(t)$ is the glucose concentration at time t, $x(t)$ is the original glucose concentration, and $n(t)$is the random noise, assumed to be additive. Filtering is used to get back $x(t)$ from $y(t)$. If the predicted spectral specifications of

noise are known, for example, if noise is white, then low-pass filtering can be used to remove noise. Since signal and noise spectra normally overlap, there is a major problem of using low-pass filteringin removing the random noise $n(t)$ from the determined signal $y(t)$ without affecting $x(t)$.Particularly, delay is the result of distortion and affects the estimated $x(t)$ with respect to the original $x(t)$. With the increase of filtering, the delay is also increased. This paper therefore suggests noise removal using a KF[8].

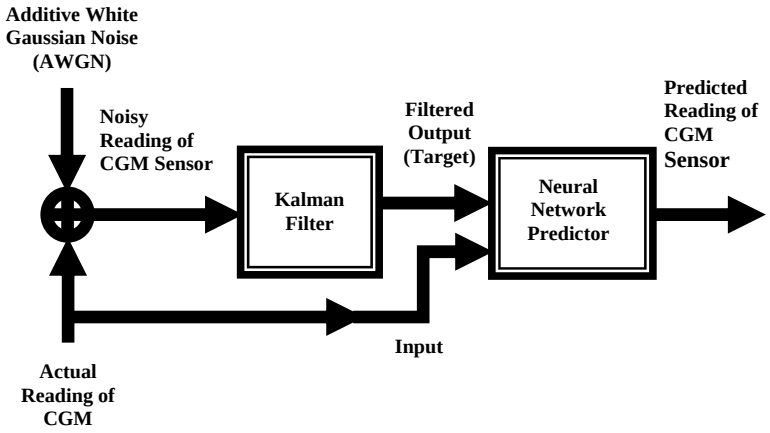

Fig. 1 Block diagram of blood glucose prediction system

4. Prediction of glucose concentration using a neural network

This research uses time-lagged feed-forward NN. The network was trained using back propagation algorithm. The training of NN stops after 1000 epochs or if the mean squared error was less than 0.1[11].

In this network, the input is the filtered CGM data. Input layer contains input neurons equal to 720 glucose levels for each patient, hidden layer contains 10 neurons, and output layer represents the predicted CGM data that also includes 720 new glucose levels after prediction.

The model of neural network used here was developed with predictive windows equal to 60and 120 minutes. Each glucose value was collected every minute. During theprocess, the dataset is divided into three groups: 70% of data is used for training, 15% forvalidation and 15% for testing the NN. Figure 2 shows the predicted data for a given CGM time-series (prediction length is 60 minutes).

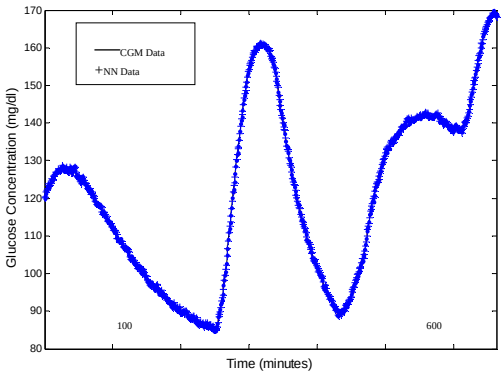

Fig 2.Predicted CGM time-series

5. Quantitative analyses

This section presents the quantitative analyses of the glucose prediction system. Data used here are 25sets of simulated blood glucose concentrations for 25 patients with various weights (25, 35,45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 115, 120, 125, 130, 135,140, 145, 150,155, 160kilograms).For all analyses, simulation period is equal to 720 minutes (or 12 hours)and Kalman filter Q and R values are equal to 1.

5.1. Methods of performance analysis

Five methods are implemented to investigate the accuracy and validity of the system.The aim of all methods is the evaluation of the mean absolute difference percent (**MAD**%) ofthe NN'spredictions. First, absolute difference percent (***AD***%) of eachpatient must be determined. Equation 2 is used to calculate the ***AD***% between predicted and the corresponding actualCGM value.

$$\boldsymbol{AD}\%(\boldsymbol{t}) = \frac{\boldsymbol{NN(t)-CGM(t)}}{\boldsymbol{CGM(t)}}\boldsymbol{x100}\% \quad (2)$$

where $AD\%(t)$ is the $AD\%$calculated at time t, $NN(t)$ is the predicted glucose value at time t, $CGM(t)$ is the actual CGM value at time t, and N is the total number of data points. Equation 3 is, finally, used to calculate the mean of all obtained $AD\%$ values, namely$MAD\%$ (note that low $MAD\%$ values are desired[11]).

$$MAD\% = \frac{\sum_{i=1}^{N} AD\%(t)}{N} \quad (3)$$

5.2. Effect of denoising

This method compares predicted CGM glucose concentrations of the suggested system withthose by a system that contains NN only. For each system, the NN isfirst trained using entire dataset of 25 patients and then ***MAD***% value of each patient isdetermined. Table 1 shows the average ***MAD***% values for entire 25 patients. It can be observedthat the proposed system has lower average ***MAD***% values for both prediction windows. Thisemphasizes the importance of having a filter in such a system.

Table 1. Effect of denoising

System	Prediction Window of 60 min.	Prediction Window of 120 min.
	MAD_{avg}%	**MAD_{avg}%**
NN with KF	29.10	33.08
NN	55.19	58.78

5.3. Variation of training set and prediction window length

This method involves analysis of the suggested system with variable training set andprediction window lengths. In this analysis, training sets using 10 to 24 patients are used forthe NN with predictive windows of 60 and 120 minutes. Performance of NN is evaluated using diabetes data for patients who are not included in the training data.Average ***MAD***% values of these patients are tabulated in table 2.

Table 2. Effects of varying the training set and the predictive window length

No. of Patients in a Training Set	Prediction Window of60 min.	Prediction Window of120 min.
	MAD_{avg}%	**MAD_{avg}%**
10	24.02	40.14
12	25.10	37.43
14	27.86	38.09

16	27.95	38.31
18	27.17	36.60
20	26.88	35.65
23	27.50	34.45
24	27.42	33.86

It is observed that average $MAD\%$ values are relatively constant for differenttraining sets when prediction window is smaller (this is contrary to what could have been expected, which is, increasing the training dataset should give better NN performance). However, as theprediction window is increased, there is an increase in all average $MAD\%$ values (that isthe accuracy of the system decreases). However,as thenumber of patients in the training set is increased, the accuracy seems to have increased a bit as well.

5.3.1. Effect of body weight

It is known that weight can influence diabetes and diabetes can influence weight. Hence, itbecomes important to control body weight fluctuations for people with diabetes. This analysisaims to check if the system is suitable for blood glucose concentration prediction ofvarious groups of patients with different body weights. Glucose concentration data of 25patients are first used to train the NN and then four groups of patients are used tocheck the system's accuracy: Group 1 contains 25 patients of average weight of 96.60kilograms; Group 2 represents 8 patients with an average weight of 50.63 kilograms (i.e. lightweight patients); Group 3 contains 9 patients with an average weight of 96.67 kilograms (i.e.medium weight patients) and Group 4 contains 8 patients with an average weight of 142.50kilograms (i.e. heavy weight patients). Table 3 lists the average $\boldsymbol{MAD\%}$ results of thisanalysis.

Table 3. Effect of patients' weight in a training set

Patients Group	**Prediction Window of 60 min.**	**Prediction Window of 120 min.**
	MAD_{avg}%	**MAD_{avg}%**
Group 1	29.10	33.08
Group 2	25.52	39.16
Group 3	24.31	36.70
Group 4	23.89	30.08

It can be seen from the results of groups 2 to 4 that when prediction window is smaller,patients' weights almost have no effect on the accuracy of the system. However, increasingthe number of patients tested has decreased the accuracy (as in group 1). This proves that thesystem may not be tested on high number of patients after it has been trained. The accuracy has decreased, as expected, for the higher prediction window.

5.3.2. Effect of exercising

Exercise is a key to lifetime management of diabetes. This method analyzes the impact ofexercise on glucose concentration prediction. Patients in group 3 of the previous analysis(section 6.3) are now exercised for periods of 30, 60, and 90 minutes. The NN istrained with the dataset of 25 patients and analysis results of patients in group 3 for 60 minuteprediction window are given in table 4.

Table 4. Effect of exercising

Patient Group	**Duration of Exercise**	**MAD_{avg}%**
Group 3	30 min.	24.04
	60 min.	38.68
	90 min.	42.45

It is observed that increasing the exercise period dramatically decreases the accuracy of thissystem due to a temporary sharp decrease of patients' blood glucose concentrations duringexercising.

5.3.3. Effect of lifestyle of a patient

Hypoglycemia can suddenly occur in people using insulin if too little food is eaten, if a meal is delayed or in the case of too much exercise. On the other hand, hyperglycemia can occur when too much food is eaten or not enough insulin is taken. Therefore, how a patient lives his/her life is often crucial in keeping diabetes under control. It is hence the intent of this analysis to see theeffects of a combination of factors such as meal intake, exercise and insulin injection on theaccuracy of the performance of this system. The NN is, again, trainedwith the dataset of 25 patients and is tested on a single patient. Table 5 shows the results.

Table 5. Effect of a patient's lifestyle

Action	**MAD_{avg}%**
Increase Meal Intake	26.23
Exercise and Increase Meal Intake	44.42
Increase Insulin Dosage	25.91
Exercise and Increase Insulin Dosage	16.05

Average $MAD\%$ values are consistent here, except when the patient has exercised as well asconsumed more food. In that case, the accuracy has decreased due possibly to suddenhypo/hyperglycemic events.

6. Conclusions

This research analyzes how a patient's body weight, his/her exercise period and lifestyle may effect glucose level prediction in humans with type 2 diabetes. It uses a hybrid technique which comprises of a Kalman filter to initially remove noise from glucose concentration, and a back propagation NN to predict new glucose concentration level up to two hours.

Prediction results show that there is an increase in $MAD\%$ valueswhenever there is an increase in prediction window length. This indicates that it is better forpatients to use small prediction windows during the measurement process to get accurateprediction results and avoid the two dangerous blood glucose levels, hyperglycemia andhypoglycemia. Results further show that the following cases should be avoided as theydecrease the prediction accuracy: testing the system after extended periods of exercisingand after when excessive exercising is also combined with increased food consumption.

This research can be improved to also cope with person to person or sensor to sensor SNR variations.

Note

This work is the product ofHanan B. Ahmed's 2013 MSc. thesis, which was completed under the supervision of Dr. A. Serener.

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