Effects of external factors in CGM sensor glucose concentration prediction

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Abstract

It is naturally desirable to avoid hypo/hyperglycemic events and commercial 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 as part of a continuous glucose monitoring (CGM) device. With the help of a Kalman filter, glucose concentration is first reduced of its random noise component, and a neural network is then used for prediction of glucose up to two hours. Finally, this system is thoroughly tested for accuracy against various external factors. It is shown that such factors as patient’s body weight, his/her exercise period and lifestyle may influence how well glucose concentration is predicted and therefore should be taken into account for early and accurate detection of hypo/hyperglycemic episodes.

1. Introduction

Diabetes mellitus is a 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, which analyzed the enhancement in CGM sensors' 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. suggested an improved proportional integral derivative (PID) control approach for blood glucose management. Stemmann et al. 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 Knobbe and Buckingham. Most favorable estimation with the aid of KF has been done by Palerm et al., where they aimed to predict the glucose trend in detecting hypoglycemia. Kuure-Kinsy et al. employed dual rate KF for real-time CGM in order to improve its calibration. The topic of denoising CGM has been more extensively tackled by Facchinetti et al., who have proposed a method based on a Bayesian estimation by a KF. They also suggested a new online approach to denoise CGM signals using a KF, whose unknown parameters are tuned to an individual.

Savage et al. formed an artificial neural network (ANN) to figure out the CGM sensor output plus the system parameters, and showed a relationship between them and blood glucose levels. A supervised back propagation neural network (BPNN) network was used for obtaining blood glucose in diabetic patients by Ashok et al. Pappada et al. utilized NeuroSolutions software to make different neural network (NN) models with variable predictive windows.

Facchinetti et al. introduced again a new technique for noise reduction that is able to deal also with the intra-individual varying of the signal to noise ratio (SNR). Shanthi and Kumar studied in their research the removal of errors caused by different 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. aimed in their work to build up a new short-term glucose prediction system based on a NN.

Panteleon and colleagues improved the calibration of CGM with the aid of a seventh order FIR filter. Keenan and associates studied the delays in two different CGM devices, by a demonstration analysis of the data set to determine a modern calibration algorithm utilized in the Paradigm Veo insulin pump. An integral based fitting and filtering algorithm for a CGM signal was developed by Chase et al.

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 NN is used to implement a prediction system for the filtered glucose concentration.

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, 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 and reduce this error, digital filtering techniques are used. In more strict terms, if following equation is considered,

$$ y(t) = x(t) + n(t) $$  \hspace{1cm} (I)

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 filtering in 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.

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\[ \text{KF} \]

\[ n(t) \] \to \text{Predicted reading of CGM sensor} \]

\[ x(t) \] \to \text{Actual reading of CGM} \]

\[ \text{Input} \]

\[ \text{Neural Network Predictor} \]

\[ \text{Filtered output (Target)} \]

\[ \text{Noisy reading of CGM sensor} \] \to \text{Kalman Filter} \]

\[ \text{Additive White Gaussian Noise (AWGN)} \]

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 0.11.

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 60 and 120 minutes. Each glucose value was collected every minute. During the process, the dataset is divided into three groups: 70% of data is used for training, 15% for validation 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 25 sets 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, 160 kilograms). 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\%) of the NN’s predictions. First, absolute difference percent (AD\%) of each patient must be determined. Equation 2 is used to calculate the AD\% between predicted and the corresponding actual CGM value.

\[
AD\%(t) = \frac{NN(t) - CGM(t)}{CGM(t)} \times 100\%
\]  

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). 

\[
MAD\% = \frac{\sum_{i=1}^{N} AD\%(t)}{N}
\]

5.2. Effect of denoising

This method compares predicted CGM glucose concentrations of the suggested system with those by a system that contains NN only. For each system, the NN is first trained using entire dataset of 25 patients and then \(AD\%\) value of each patient is determined. Table 1 shows the average \(AD\%\) values for entire 25 patients. It can be observed that the proposed system has lower average \(AD\%\) values for both prediction windows. This emphasizes the importance of having a filter in such a system.

<table>
<thead>
<tr>
<th>System</th>
<th>Prediction Window of 60 min. MAD%</th>
<th>Prediction Window of 120 min. MAD%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NN with KF</td>
<td>29.10</td>
<td>33.08</td>
</tr>
<tr>
<td>NN</td>
<td>55.19</td>
<td>58.78</td>
</tr>
</tbody>
</table>

5.3. Variation of training set and prediction window length

This method involves analysis of the suggested system with variable training set and prediction window lengths. In this analysis, training sets using 10 to 24 patients are used for the 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>
<thead>
<tr>
<th>No. of Patients in a Training Set</th>
<th>Prediction Window of 60 min. MAD%</th>
<th>Prediction Window of 120 min. MAD%</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>24.02</td>
<td>40.14</td>
</tr>
<tr>
<td>12</td>
<td>25.10</td>
<td>37.43</td>
</tr>
<tr>
<td>14</td>
<td>27.86</td>
<td>38.09</td>
</tr>
</tbody>
</table>
It is observed that average MAD\% values are relatively constant for different training 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 the prediction window is increased, there is an increase in all average MAD\% values (that is, the accuracy of the system decreases). However, as the number 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, it becomes important to control body weight fluctuations for people with diabetes. This analysis aims to check if the system is suitable for blood glucose concentration prediction of various groups of patients with different body weights. Glucose concentration data of 25 patients are first used to train the NN and then four groups of patients are used to check the system’s accuracy: Group 1 contains 25 patients of average weight of 96.60 kilograms; 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 142.50 kilograms (i.e. heavy weight patients). Table 3 lists the average MAD\% results of this analysis.

<table>
<thead>
<tr>
<th>Patients Group</th>
<th>Prediction Window of 60 min.</th>
<th>Prediction Window of 120 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAD_{avg}%</td>
<td>MAD_{avg}%</td>
</tr>
<tr>
<td>Group 1</td>
<td>29.10</td>
<td>33.08</td>
</tr>
<tr>
<td>Group 2</td>
<td>25.52</td>
<td>39.16</td>
</tr>
<tr>
<td>Group 3</td>
<td>24.31</td>
<td>36.70</td>
</tr>
<tr>
<td>Group 4</td>
<td>23.89</td>
<td>30.08</td>
</tr>
</tbody>
</table>

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, increasing the number of patients tested has decreased the accuracy (as in group 1). This proves that the system 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 of exercise 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 is trained with the dataset of 25 patients and analysis results of patients in group 3 for 60 minute prediction window are given in table 4.

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Duration of Exercise</th>
<th>MAD_{avg}%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 3</td>
<td>30 min.</td>
<td>24.04</td>
</tr>
<tr>
<td></td>
<td>60 min.</td>
<td>38.68</td>
</tr>
<tr>
<td></td>
<td>90 min.</td>
<td>42.45</td>
</tr>
</tbody>
</table>
It is observed that increasing the exercise period dramatically decreases the accuracy of this system due to a temporary sharp decrease of patients’ blood glucose concentrations during exercising.

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 the effects of a combination of factors such as meal intake, exercise and insulin injection on the accuracy of the performance of this system. The NN is, again, trained with the dataset of 25 patients and is tested on a single patient. Table 5 shows the results.

<table>
<thead>
<tr>
<th>Action</th>
<th>MAD avg %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase Meal Intake</td>
<td>26.23</td>
</tr>
<tr>
<td>Exercise and Increase Meal Intake</td>
<td>44.42</td>
</tr>
<tr>
<td>Increase Insulin Dosage</td>
<td>25.91</td>
</tr>
<tr>
<td>Exercise and Increase Insulin Dosage</td>
<td>16.05</td>
</tr>
</tbody>
</table>

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

6. Conclusions

This research analyzes how a patient’s body weight, his/her exercise period and lifestyle may affect 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% values whenever there is an increase in prediction window length. This indicates that it is better for patients to use small prediction windows during the measurement process to get accurate prediction results and avoid the two dangerous blood glucose levels, hyperglycemia and hypoglycemia. Results further show that the following cases should be avoided as they decrease the prediction accuracy: testing the system after extended periods of exercising and 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 of Hanan B. Ahmed’s 2013 MSc. thesis, which was completed under the supervision of Dr. A. Serener.

References


