Prediction of blood glucose levels and nocturnal hypoglycemia using physiological models and artificial neural networks

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Abstract

Blood glucose control is a burden for subjects who live with Type 1 Diabetes (T1D). Patients with T1D aim to maintain blood glucose levels into euglycemic ranges, but this is not trivial task and requires a lifelong commitment on diabetes management. Emerging technologies (e.g. continuous glucose monitoring, insulin pump, mobile applications) have permitted to track several signals related with diabetes management closely, boosting the application of various machine learning algorithm focusing to learn the behavior of blood glucose. In this work we present the application of artificial neural networks to perform two different tasks: i) creating regression models to predict blood glucose levels continuously and ii) creating classification models to predict nocturnal hypoglycemic events. Both methods are evaluated on a dataset which contains about eight weeks of data from six different patients with T1D. Numerical results indicate that ANNs are feasible to perform these tasks satisfactorily and may be considerable to assist patients on T1D diabetes management.

1 Introduction

Regulating blood glucose (BG) levels is a lifelong challenge for those who live with Type 1 Diabetes (T1D). Due to an autoimmune disease, the pancreas stops to produce insulin drastically, enforcing subjects to inject it exogenously. In addition to insulin injection, subjects must have acute self-management skills to improve BG control, such as counting the amount of carbohydrates (CHO) in meals and measure BG levels constantly.

Although emerging diabetes technologies achieved remarkable success in the last decade, so far there is not any commercial fully-automated system that completely withdraw the burden from patients of taking daily decisions regarding diabetes management. The prediction of blood glucose levels in advance permits subjects to take preventive actions before the occurrence of adverse events, reducing the risk of short- and long-term complications. In addition, the prediction of specific events (e.g. nocturnal hypoglycemia) can improve subjects' safety, once it allow the development of specialized prediction algorithms, that may work in parallel with the continuous BG level prediction algorithm.

Artificial neural networks (ANNs) are able to acquire and maintain knowledge based on information, simulating the human brain [Haykin, 2009; Bishop *et al.*, 1995] and have been widely applied successfully on several regression and classification problems. The utilization of ANN to predict BG levels have been used for the last two decades [Sandham *et al.*, 1998] and even these days it is used in new studies due to its great capacity to model the different non-linearities in glucose dynamics. Since continuous glucose monitoring (CGM) devices have been launched, CGM historical data are used by data-driven models to predict BG levels, nevertheless, the use of additional inputs (such as meal consumption and insulin delivery) is able to improve prediction performance [Zecchin *et al.*, 2016].

This paper presents two different tools that may be used by subjects to support daily decisions regarding diabetes management using ANN and physiological models: i) a tool to provide prediction of BG levels continuously and ii) a tool to predict the occurrence of nocturnal hypoglycemic events. The work has been conducted through the software MATLAB.

2 Methods

This section presents the dataset and the methodologies applied for the prediction of BG levels and nocturnal hypoglycemic events.

2.1 Database

The dataset used for the developing of the blood glucose prediction algorithms was the OhioT1DM dataset [Marling and Bunescu, 2018]. It contains data of six individuals with T1D, under insulin-pump therapy, wearing CGM, physical activity band and reporting life-event data through a smart-phone app throughout the 8-week data collection period.

More information regarding the devices used by patient, data format and patients' characteristics can be found elsewhere [Marling and Bunescu, 2018].

Table 1: Parameters used in the physiological models.

Parameter	Value
K_{DIA}	0.0182
C_{bio}	0.8
t_{max}	60
k_s	0.0115

2.2 Physiological models

Insulin On Board (IOB)

The Insulin on board (IOB) represents the insulin that has already been inject in the body and is still active. The IOB is computed based on the insulin accumulated in two compartments C_1 and C_2 [Wilinska *et al.*, 2005].

$$\begin{aligned} \dot{C_1}(t) &= u(t) - K_{DIA}C_1(t) \\ \dot{C_2}(t) &= K_{DIA}(C_1(t) - C_2(t)) \\ IOB(t) &= C_1(t) + C_2(t) \end{aligned} \tag{1}$$

where u is the insulin injected and K_{DIA} is a constant related with the duration of insulin action (DIA).

Carbohydrates on Board (COB)

Similarly to IOB, carbohydrates on board (COB) represents the remaining CHO amount of a meal that has not yet appeared in the blood as glucose. It is an extension of the model which describes the rate of appearance (R_a) of glucose in the blood due to CHO intake [Hovorka *et al.*, 2004].

$$\begin{aligned} R_a(t) &= \frac{C_{in}\, C_{bio}\, t\, e^{(-t/t_{max})}}{t^2_{\max}} \\ COB(t) &= C_{in}C_{bio} - \int_{t_{meal}}^{t} R_a(t)dt \end{aligned} \tag{2}$$

where C_{in} is the amount of CHO ingested, C_{bio} is the bioavailability, t_{max} denotes the time of the maximum appearance rate of glucose in the accessible glucose compartment and t_{meal} is the time instant which a meal is consumed.

Activity on Board (AOB)

The activity on board (AOB) is computed using the information related with the total steps performed throughout the day [Ozaslan *et al.*, 2017]. The total number of steps performed over each sampling time is weighted by an exponential decay curve:

$$AOB(t) = steps(t)e^{(-k_s t)} \tag{3}$$

where steps(t) is the total number of steps performed at time instant t and k_s is a constant related to the duration of the effects of physical activity on blood glucose control. One AOB curve is obtained for each time instant t, and the final value of the AOB represents the superposition of all the curves. The parameters considered for the physiological models in this work are presented in Table 1.

2.3 Regression models for continuous prediction of blood glucose level

The continuous prediction of BG levels aims to predict future BG values, allowing subjects to anticipate harmful situations by taking correction actions in advance. ANN are considered to create individualized models, which are based on glucose, insulin, carbohydrate and physical activity data.

Table 2: Rules to select in which subset R an instance should be classified according to $CGM(t_0)$.

r_j	Conditions*
1	$CGM(t_0) < 54$
2	$54 \leq CGM(t_0) < 70$
3	$70 \leq CGM(t_0) < 120$
4	$120 \leq CGM(t_0) < 180$
5	$180 \leq CGM(t_0) < 250$
6	$CGM(t_0) \geq 250$

* values are considered in mg/dL.

Table 3: Parameters considered during the ANNs' training process for regression models.

Training algorithm	Levenberg-Marquardt
Performance Function	mean square error
Number of inputs	5
Number of units - hidden layer	8
Activation function - hidden layer	Hyperbolic tangent
Number of units - output layer	1
Activation function - output layer	Linear

Consider the datasets S described in 2.1 with k samples. For each subject, $S = \{(x_i, y_i)\}$, $i = 1, ..., k$, where $x_i \in X$ is a sample in the q-dimensional feature space $X = \{f_1, f_2, ..., f_q\}$, and $y_i \in Y = \{target\}$ is the desired target output. Furthermore, S has been divided into two subsets: S_{train} representing the m instances considered for training and S_{test} the remaining n instances considered for testing, so $S_{train} \cup S_{test} = \{S\}$ and $m + n = k$. S_{test} is composed by approximately the final 10 days of S, and the previous days were located in S_{train}.

Feature subspace is composed by CGM measurements and also by informations obtained from the physiological models presented in 2.2. In total, five features were considered (q=5): $CGM(t_0)$, $C\dot{G}M(t_0)$, $COB(t_0)$, $IOB(t_0)$ and $AOB(t_0)$, where $C\dot{G}M(t_0)$ is computed as $\frac{CGM(t_0) - CGM(t_0-5)}{5}$. Finally, $CGM(t_0$+PH) was determined as target value and PH is the prediction horizon. Thereon, all the m instances were divided again into a subset r_j ($j = 1, ..., R$), based on the value of $CGM(t_0)$ in each instance. Table 2 shows the rules to select in which subset r an instance should be located. Instances without $CGM(t_0)$, $C\dot{G}M(t_0)$ or $CGM(t_0$+PH) data were discarded in both S_{train} and S_{test}.

Each one of the r subsets were used separately to train feed-forward ANNs. For convenience, all the ANN have identical hyper-parameters, presented in Table 3. Firstly, these parameters were tuned using k-fold cross validation for PH = 30 minutes, and the same parameters were replicate for PH = 60 minutes. After the end of the training procedure of all r subsets, a group of five regression models was generated for every r subset. Each one of the n instances located in S_{test} was evaluated in only one group of the R regression models produced. The selection of which group of regression models should be used was based on $CGM(t_0)$ and the conditions presented in Table 2. Thus, each group generated five

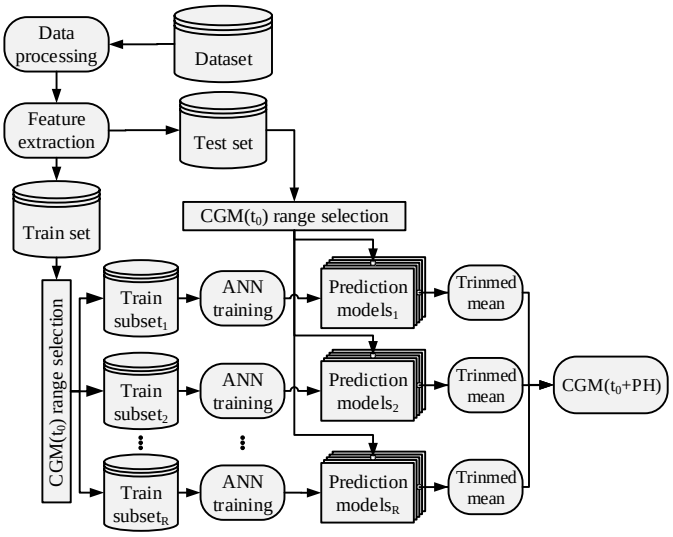

Figure 1: Methodology considered to generate regression models for BG levels prediction.

values of $CGM(t_0 + PH)$, that were later post-processed. The minimum and maximum of those five values were discarded, and the average of the remaining three intermediate values was computed (trinmed mean), resulting in the final predicted value. This value was bounded between 40 mg/dL and 400 mg/dL. Figure 1 summarizes the methodology for BG level prediction.

The performance was evaluated by the root mean square error (RMSE) between the predicted value ($\hat{y}$) and the target (y).

$$RMSE = \sqrt{\frac{1}{n}\sum_{a=1}^{n}(\hat{y}_a - y_a)^2} \quad (4)$$

2.4 Classifications models for nocturnal hypoglycemia prediction

The prediction of nocturnal hypoglycemic events is considered as a two-class classification problem in this work. The aim of such classification models are to inform subjects regarding the possibility of the occurrence of low BG levels while subjects are sleeping. With such information, subjects may be able to act pro-actively to avoid such adverse situation by consuming snacks or reducing insulin infusion for the following night period. Subjects must inform that they are preparing to sleep (sleep announcement - t_{sleep}). Then the system may be able to predict the possibility of hypoglycemia in the following hours, based on daily activities performed by the subject.

Similarly as presented in 2.3, dataset S has been divided into Z_{train} and Z_{test}, with Z_{test} containing the last 10 nights from S and the remaining data has been located in Z_{train}. For such classification problem, $S = \{(\lambda_i, \chi_i)\}$, $i = 1, ..., h$, where $\lambda_i \in \Lambda$ is a sample in the Q-dimensional feature space $\Lambda = \{f_1, f_2, ..., f_Q\}$, and χ_i is a class identity label associated with the instance λ_i.

Table 4: Distributions of instances in Z_{train} and Z_{test} for the six subjects.

Patient ID	Instances in Z_{train} (Class 0 / Class 1)	Instances in Z_{test} (Class 0 / Class 1)
#559	35 (26/9)	7 (4/3)
#563	27 (23/4)	7 (7/0)
#570	34 (32/2)	9 (9/0)
#575	37 (31/6)	10 (8/2)
#588	43 (38/5)	10 (9/1)
#591	37 (33/4)	8 (8/0)

Table 5: Parameters considered during the ANNs' training process for classification models.

Training algorithm	Scaled conjugate gradient
Performance Function	Cross-entropy
Number of inputs	22
Number of units - hidden layer	16
Activation function - hidden layer	Hyperbolic tangent
Number of units - output layer	1
Activation function - output layer	Logarithmic sigmoid

Subjects self-reported the beginning and the ending of sleep period. The time-stamp related with the beginning of sleep period was determined as t_{sleep}. Feature subspace is composed by the 22 features (Q=22). Inputs related to glucose data were the CGM value at t_{sleep}, hourly average of CGM readings over the last six hours before t_{sleep}, hourly area under the curve below 70 mg/dL of CGM readings over the last six hours before t_{sleep}, and rate of change (ROC) of CGM readings during the previous 30 minutes before t_{sleep}. In addition, the values of the COB, AOB, and IOB at t_{sleep} were also included. The six-hour period following t_{sleep} was used to assign the class of the respective instance. Class 1 was assigned (i.e. indicating hypoglycemia) if any of following situations were identified: 1) three consecutive CGM readings below 70 mg/dL, 2) any self-monitoring blood glucose (SMBG) performed during this period bellow 70 mg/dL, 3) subjects consumed CHO to treat hypoglycemia (i.e. a meal tagged as hypoglycemia rescue). Otherwise, if none of the previous conditions occurred, the instance was labeled as Class 0.

Instances were excluded in both training and testing datasets in case of more than 25% of CGM missing data for the six previous hours before t_{sleep} or in case than more than 25% of CGM missing data in the following six hours of prediction, after t_{sleep}. Table 4 presents the total amount of instances obtained in each set.

Individualized classification models were built considering the parameters in Table 5. Models hyper-parameters were optimized using k-fold cross validation. Due to the intrinsic characteristics of the dataset, an imbalance between classes can be notice in both Z_{train} and Z_{test}. To deal with such problem, the adaptive synthetic sampling algorithm [He and Garcia, 2009] has been considered during the training process. Performance was analyzed according to the metrics presented in Table 6.

Table 6: Metrics to assess the performance of the classification models.

Accuracy	$\frac{TP+TN}{TP+FN+TN+FP}$
Sensitivity	$\frac{TP}{TP+FN}$
Specificity	$\frac{TN}{TN+FP}$

TP: true positive; TN: true negative; FP: false positive; FN: false negative.

Table 7: RMSE results for the regression models for the test dataset.

Patient ID	PH=30	$PH = 60$
#559	18.83	32.52
#563	19.43	31.33
#570	15.88	27.48
#575	22.86	35.28
#588	17.84	30.12
#591	21.12	33.60
AVG	19.33	31.72

3 Results

This section presents the results for both methodologies described in 2.3 and 2.4. Results for continuous BG prediction considering two different PH are presented in Table 7. In addition, Figure 2 shows the predictions performed during the first day of S_{test} for Patients #570 and #575. Results regarding the performance of the classification models are presented in Table 8.

4 Discussion

The results achieved with the ANN for short-time BG prediction are similar (in terms of RMSE) with a study which considered a recursive ANN [Mirshekarian *et al.*, 2017]. Another study [Zecchin *et al.*, 2012] also considered ANN and meal absorption model to predict BG levels, achieving better results (RMSE $\approx$ 14 mg/dL for PH = 30) in data from real patients. However, further comparisons regarding results should be performed when different methods are evaluated with the same dataset.

As demonstrated by [Zecchin *et al.*, 2016], the inclusion of physiological signals contributes to improve continuous BG predictions. In this work, in addition to COB and IOB, we also included the effects of physical activities (represented by the signal AOB) as input of the models. As well known, physical activity plays an important role in BG regulation in T1D [Riddell *et al.*, 2017], but there are few works that address the use of physical activity signals in BG levels prediction.

The continuous prediction is intended to support patients decisions in case of hyper- or hypoglycemia prediction. However, while subjects are sleeping, it is not possible to follow the continuous predictions. Therefore, it is necessary for the subject to be awakened by some alarm whether necessary, impairing in subjects' quality of life. The prediction of nocturnal hypoglycemic events allows subjects to anticipate dangerous situations without the need to be awakened.

Table 8: Performance metrics for the classification models for the test dataset. Results are shown in percentage.

Patient ID	Sensitivity	Specificity	Accuracy
#559	66.67	75	71.43
#563	–	100	100
#570	–	88.89	88.89
#575	50	87.50	80
#588	100	100	100
#591	–	100	100

The occurrence of nocturnal hypoglycemic events are associated with activities performed in the previous day [Metcalf *et al.*, 2014; Bachmann *et al.*, 2016]. In this work, we considered different inputs aiming to learn the effects of these inputs in the behavior of BG during overnight. Results indicate the feasibility to obtain classification models able to predict hypoglycemia during overnight. Based on this information, patients can take preventive actions to increase their safety. In case of prediction of hypoglycemia, individuals may consume a snack prior to sleep. Such tool is more advantageous for patients whose are not under sensor-augmented pump therapy or under closed-loop therapy. Patients who are under multiple-daily injections (MDI) therapy or under conventional pump therapy do not have any tool to assist them to avoid hypoglycemia during overnight. Therefore, a tool similar to the one presented in this paper can be very helpful to increase users' safety.

The results obtained by the classification models indicate the feasibility of such approach. Although some patients do not have experienced hypoglycemia in the days used to test the models, outcomes obtained by other patients are satisfactory. An important remark regarding this dataset is that patients' insulin pump had threshold suspend feature. Such feature allows the pump to stop insulin delivery when BG drop a pre-set threshold. Clinical results showed that this feature can reduce the time spent in hypoglycemia, especially during the night [Ly *et al.*, 2013]. Therefore, it is expected that the methodology presented in this study will have a greater impact on patients who actually have hypoglycemia during night, like MDI users.

5 Conclusions

Two different prediction tools for T1D management were presented in this paper considering ANN. The first one has been developed to provide short-time prediction of BG levels. The second tool aimed to predict nocturnal hypoglycemic events based on classification models. Results of both tools showed that ANNs appear to be suitable to perform satisfactorily these tasks and can be used in decision support system to assist patients with T1D to improve BG control and safety.

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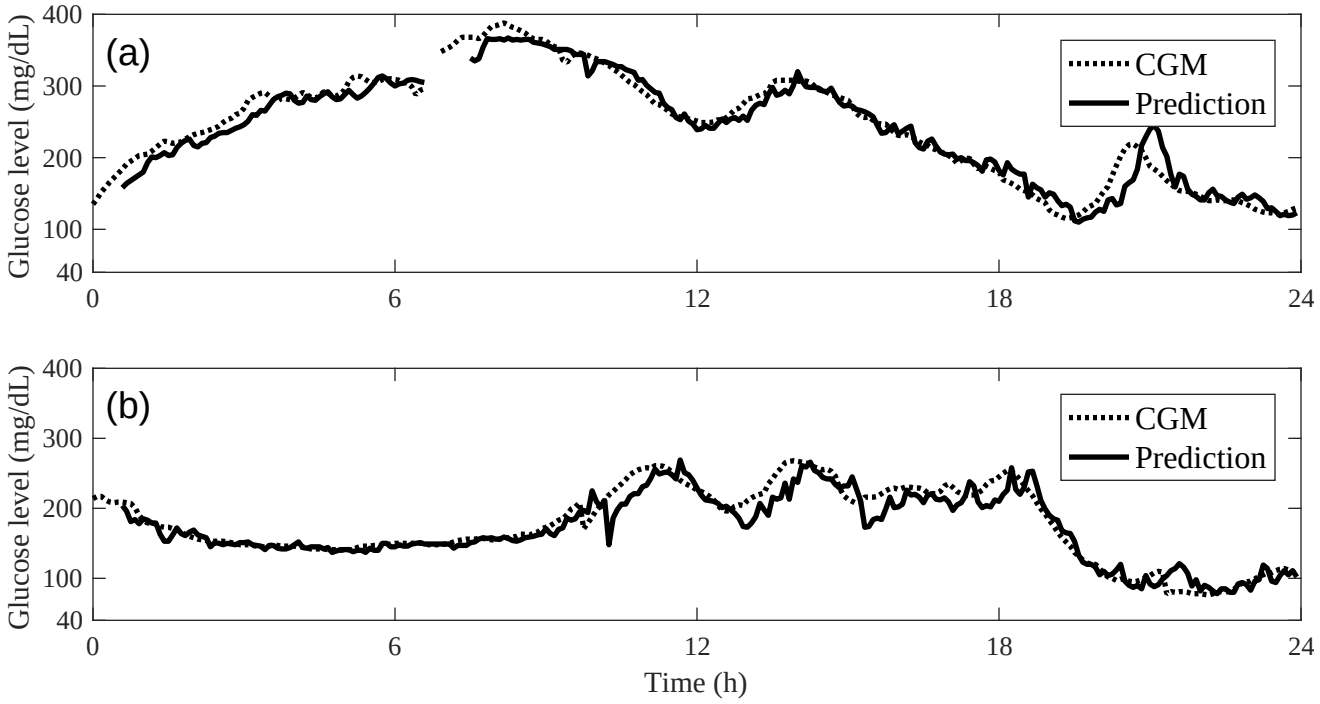

Figure 2: Comparison between CGM readings and predictions performed during the first 24-h of S_{test} considering $PH = 30$ minutes. (a) patient #570 and (b) patient #575.

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