A new neural network approach for short-term glucose prediction using continuous glucose monitoring time-series and meal information.

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A New Neural Network Approach for Short-Term Glucose Prediction Using Continuous Glucose Monitoring Time-Series and Meal Information

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***Abstract*— In the last decade, improvements in diabetes daily management have become possible thanks to the development of minimally-invasive portable sensors which allow continuous glucose monitoring (CGM) for several days. In particular, hypo and hyperglycemia can be promptly detected when glucose exceeds the normal range thresholds, and even avoided through the use of on-line glucose prediction algorithms. Several algorithms with prediction horizon (PH) of 15-30-45 min have been proposed in the literature, e.g. including AR/ARMA time-series modeling and neural networks. Most of them are fed by CGM signals only. The purpose of this work is to develop a new short-term glucose prediction algorithm based on a neural network that, in addition to past CGM readings, also exploits information on carbohydrates intakes quantitatively described through a physiological model. Results on simulated data quantitatively show that the new method outperforms other published algorithms. Qualitative preliminary results on a real diabetic subject confirm the potentialities of the new approach.**

I. INTRODUCTION

Diabetes is a chronic disease affecting more than 250 millions of people in the world. It is characterized by elevated blood glucose, due either to the inability of the pancreas to produce insulin (type 1 diabetes), or by derangements in insulin secretion and action (type 2 diabetes). Diabetes standard therapy is mainly based on diet, physical exercise and insulin and drug administration, optimized according to the information obtained by self monitoring of blood glucose 3-4 times per day. This approach is suboptimal, and blood glucose concentration often exceeds the normal range thresholds (70-180 mg/dl). Hyperglycemia (glucose above 180 mg/dl) causes long term complications, as neuropathy, retinopathy, and cardiovascular and heart diseases; hypoglycemia (glucose lower than 70 mg/dl) may lead to risky short term events, such as diabetic coma [1].

In the last ten years, new horizons have been opened when continuous glucose monitoring (CGM) sensors have become available. They are non-invasive or minimally invasive portable devices, which allow the fine monitoring of the glycemic concentration in a quasi "continuous" way, returning high frequently measurements (e.g. one every 1-5 min) of glycemic concentration for several days (up to 14). Some CGM devices incorporate systems for the real-time generation of alarms when the measured glycemia exceeds the normal range thresholds [2]. However, it would be preferable to prevent hypo/hyperglycemia, instead of medicating it [3]. This would be possible if an alert were generated e.g. 20-30 min before the occurrence of the risky event.

Recently, several techniques, based e.g. on polynomial [4], AR/ARMA [5] [6], ARX [7], state space [8] or neural network models [9] [10] have been proposed for short term glucose prediction. Published results suggested that, with prediction horizon (PH) of 30-45 min, sufficiently accurate glucose predictions can be obtained. Notably, in [7] and [10] available information on ingested carbohydrates and injected insulin was exploited without obtaining any significant improvement over much simpler models.

The purpose of this work is to develop a new short-term (PH=30) glucose prediction algorithm based on a neural network that, in addition to past CGM readings, also exploits information on carbohydrates intakes quantitatively described through a physiological model in a smarter way.

The performance of the prediction algorithm is tested on 5 virtual patients generated in silico via a Type 1 Diabetes simulator [11] and on one real patient. Results are compared with those obtained by the first order polynomial-based [5] (hereafter referred as poly(1)) and the neural network based [9] (hereafter referred as NNPG) prediction algorithms.

II. DATA BASE

A. Simulated Data

Five virtual patients were extracted from the UVa/Padova Type-1 Diabetic Simulator [US2008/067725] [11]. For each subject, the simulation scenario consisted of 5 consecutive days of monitoring (sampling time of 1 min), with 3 meals per day. Breakfast, lunch and dinner were randomly located respectively in the time intervals $6-8$, $12-14$, and $19-21$, and consisted of 45+u, 75+u and 85+u g of carbohydrates respectively, where u is a random variable uniformly distributed in $(-10,\ 10)$, used to have more realistic simulations and account for variability in carbohydrates intake.

From each profile, a subset of samples in 3 consecutive days was extracted and used to train and validate the network, and 2 subsets of samples in 1 day were extracted and used to test the algorithm performance.

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B. Real Data

The considered real data set consists of CGM measurements (FreeStyle Navigator™, 1 min sampling time) and information on meals collected in a Type 1 diabetic volunteer for 7 consecutive days during the DIAdvisor project [12].

III. THE GLUCOSE PREDICTION ALGORITHM

A. Overall description

Previous applications of NNs to CGM prediction improved the performance of much simpler strategies, based e.g. on polynomial model of order 1, (poly(1)), or on autoregressive model of order 1 (AR(1)), only slightly, as demonstrated by comparing the results reported in [9], [10], with those of e.g. [5]. A possible explanation for this only mild improvement is that CGM data present predominantly piecewise linear components, which can be satisfactorily described even by resorting to simple linear algorithms. The direct application of NNs to predict CGM data forces them to learn both linear and non linear dynamics, mitigating their peculiar ability of modeling non linear relationships between inputs and outputs.

According to the above rationale, the prediction algorithm proposed in this study is composed by two parts: the simple poly(1) model [5], to describe linear dynamics, and a NN module, trained to correct the error committed by poly(1) (in which, ideally, only non linearities are present). For the sake of brevity, hereafter, this algorithm will be referred to as NN-LPA (NN-Linear Prediction Algorithm). The complete structure is schematized in Fig. 1.

The time-varying poly(1) model predicts the future glycemia ($\widehat{CGM}_l(t+PH)$) on the basis of the last CGM sensor readings. Past poly(1) predictions are stored for PH min, and, every time the sensor provides a new CGM reading, the error $e(t)$ between the true glycemic value, and the one forecasted by the poly(1) model PH minutes previously, is computed. This error, together with other inputs (described below), enter a feed-forward neural network trained to predict the offset between $e(t)$, and the present unknown error, that affects $\widehat{CGM}_l$. This offset is then summed to $e(t)$, to obtain an estimate of $e(t+PH)$. Finally, $\widehat{CGM}_l(t+PH)$ is combined with $\hat{e}(t+PH)$, to have a more accurate value for the expected glycemia, that would be measured by the sensor in PH min.

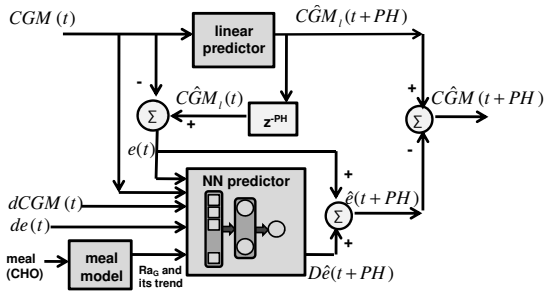

Fig. 1. Block scheme of the proposed CGM predictor.

B. NN structure

By resorting to the Matlab R2010a® Neural Networks Toolbox [13], network structure and inputs have been investigated through k-fold cross validation strategy on the training set data, obtaining a compromise between precision of the NN in fitting the training data and ability to generalize. The resulted network is totally connected and feedforward, with one hidden layer with 8 neurons, each one with tangent sigmoid activation function, and an output layer with one neuron with linear transfer function. In particular, the inputs are

- the current glucose concentration measured by the CGM sensor,
- the CGM trend, relative to the last 15 min of monitoring
- the current prediction error

$$e(t) = \widehat{CGM}_l(t) - CGM(t)$$

  where $\widehat{CGM}_l(t)$ is the CGM value, predicted 30 minutes before by the poly(1) model, and CGM(t) is the current CGM value measured by the sensor.
- the trend of the prediction error, relative to the last 15 min:
- the estimation of the future glucose rate of appearance (Ra_G) of ingested carbohydrates, computed at the time instant at which we want to predict the CGM (i.e. t+30). The rate of appearance of glucose in the blood is obtained through the model proposed in [14]
- three trend values of the future Ra_G, computed every 10 minutes.

The output $De(t)$ is the difference between the unknown error, affecting the present poly(1) prediction of CGM(t+30), and e(t) (the error committed 30 minutes previously by poly(1), forecasting the CGM value just measured by the sensor).

Inputs and output have been properly scaled, so that, at the beginning of the training procedure, all the signals have potentially the same weight, and they all belong to the linear range of the tangent sigmoid activation function of the neurons of the hidden layer.

C. NN training

Network parameters are randomly initialized and optimized through backpropagation Levenberg-Marquardt training algorithm [13], applied in a batch mode. The training procedure is stopped using cross validation, after 100 consecutive worsening of the NN performance on the validation set.

IV. RESULTS

A. Evaluation methodologies

The proposed prediction algorithm (NN-LPA), the method developed in [5] (poly(1)) and the NN implemented in [9] (NNPG) were quantitatively evaluated by computing:

- the Root Mean Square Error, RMSE, (mg/dl) between the predicted time series and the target (i.e. the glucose series measured by the CGM sensor). The RMSE is

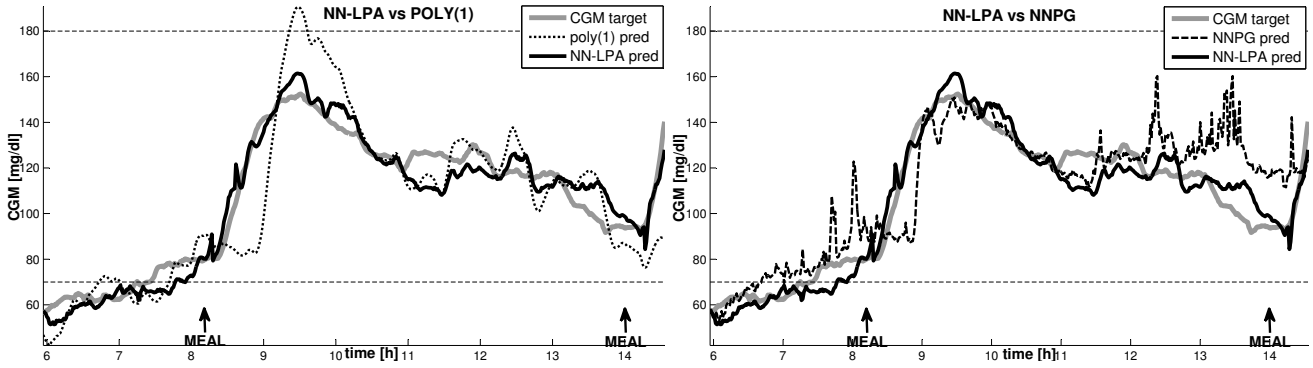

Fig. 2. A zoom of a simulated CGM series (grey continuous line), with the prediction (PH=30min)of NN-LPA (black continuous line), and the prediction of poly(1) (dotted line, left panel) and of NNPG (dashed line, right panel).

largely used to evaluate the goodness of time-series prediction [5] [9].

- the temporal gain (TG (min)), obtained as TG = PH − delay, with the delay defined as the shift that minimizes the distance between predicted and target time series. This metric was used, for instance in [5] [9]. The closer to PH, the better the TG, since future hypo/hyperglycemic events could be mitigated, or even avoided, if they are predicted sufficiently in advance.
- the "clinical usefulness" of the predicted profile, quantified with the index J [15].

B. Results on simulation

The NN-LPA, poly(1) and NNPG were all trained on the training set, and tested on an independent test set. No preprocessing (including digital filtering) of data was applied.

An example of the application of the three prediction algorithms (PH = 30 min) is displayed in Fig. 2. A detail of the time window 6:00-14:30 h is reported. By eye inspection, NN-LPA (continuous black line) performs significantly better than other methods. Focusing on the left panel (NN-LPA vs poly(1), dotted line), the accuracy of the prediction during and after a meal has been significantly improved, the RMSE has been reduced from 25.6 to 12.1 mg/dl, and the TG achieved by NN-LPA is 6 min better than the one of poly(1) (26 min vs 15 min). Moreover, NN-LPA is also more rapid in detecting changes in the sign of CGM derivative, reducing the typical overshooting that characterizes poly(1) prediction. This aspect may be important in an alarm generation context, because it would mitigate the risk of generating false alerts (consider e.g. the false hyper-alert that poly(1) would have generated around time 9:20). Focusing on the right panel, the better performance of NN-LPA with respect to NNPG (dashed line) is rather evident even by eye. The prediction obtained by NN-LPA is more accurate than NNPG in terms of RMSE (12.1 vs 16.4 mg/dl), and significantly more regular, with J equals to 9 and 353 for NN-LPA and NNPG, respectively. We recall that, according to [15], the lower J, the better the prediction.

Numerical results, reported in Table I, confirm what already seen on the representative subject of Fig. 2, i.e. NN-LPA outperforms both other methods. More importantly, the non parametric Mann Whitney U test confirms that all the improvements registered among the numeric values of the indexes are significant ($p < 0.05$), apart from the value of J relative to NN-LPA and poly(1).

The RMSE is satisfactory for both NNs, and markedly lower than for the poly(1) model. Moreover, NN-LPA is slightly, but significantly more accurate than NNPG. Considering the mean TG, NN-LPA gives about 26 minutes of net forecasting, virtually allowing patients to take countermeasures to avoid (or at least mitigate the effect of) a dangerous hypo or hyperglycaemic event, and to tune therapies accordingly with the expected future glucose. The TG of NN-LPA is significantly higher than the TG observed with the other two models (+3.7 and +14.6 min greater than NNPG and poly(1), respectively).

Finally, the mean values of the index J show that the predictions obtained with NN-LPA and with poly(1) are far more regular than the profiles forecasted with NNPG. In a patient perspective, the smoothness of the predicted time series is crucial, since oscillations can facilitate the generation of false hypo and hyper-alerts, lowering the predictor reliability.

C. Results on a real time-series

The NN-LPA was trained and tested on the CGM profile of one real patient, monitored for 7 consecutive days with the FreeStyle Navigator™ (1 min sampling time). The prediction obtained on the test series is reported in Fig. 3. As we can note in the left panel, NN-LPA (continuous black line) is more rapid than poly(1) (dotted line) in detecting

TABLE I

MEAN (± SD) RMSE, TG, AND J OBTAINED ON SIMULATED DATA, PREDICTING FUTURE CGM READINGS (PH=30MIN)

	NN-LPA	**NNPG**	**poly(1)**
RMSE [mg/dl]	9.7 ± 1.1	13.4 ± 2.4	19.4 ± 4.2
TG [min]	26.4 ± 2.9	22.7 ± 5.0	11.8 ± 1.9
J [-]	8.2 ± 1.6	201.2 ± 76.7	3.2 ± 1.0

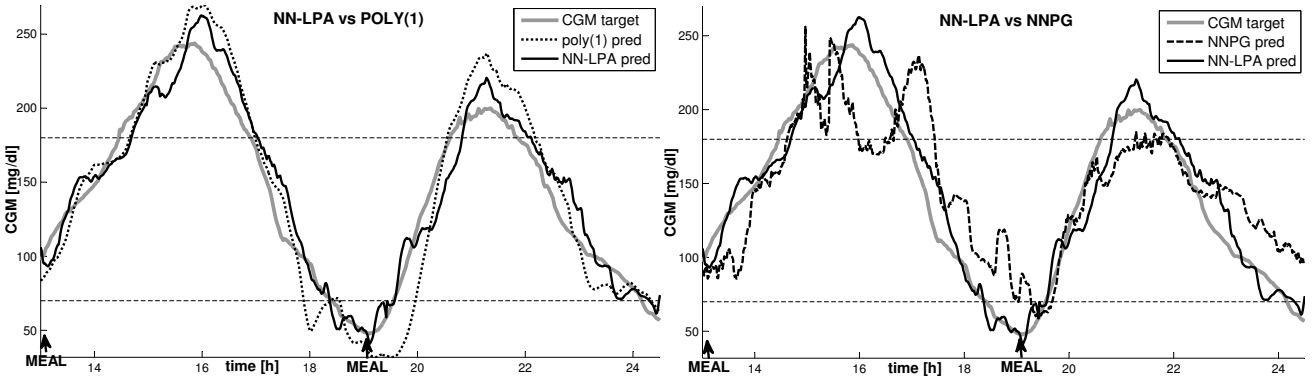

Fig. 3. A zoom of the real test-CGM series (grey continuous line), with the prediction of NN-LPA (black continuous), and the prediction (PH=30min) of poly(1) (dotted line, left panel) and of NNPG (dashed line, right panel).

changes in CGM derivatives, as observed on simulated data. Concentrating on the right panel, it is clear by eye that NN-LPA prediction is smoother than NNPG profile (dashed line), and is also far more adherent to the target CGM series. As far as numerical indexes is concerned, the RMSE results 28.2 mg/dl for NN-LPA, 40.0 mg/dl for NNPG and 30.5 mg/dl for poly(1). J is 10.0 for NN-LPA, 99.8 for NNPG and 0.8 for poly(1). No differences are reported for the TG, that is equal to 12 min for all models. These results are promising and suggest that, increasing the dataset, the new algorithm would be able to accurately predict a wide variety of glycemic dynamics, allowing to improve diabetes therapy and the goodness of glycemic control.

V. CONCLUSIONS

In this paper we presented a new algorithm, for short-term glucose prediction based on NN. The major novelties are: a) the incorporation in the prediction machinery of a physiological model able to reliably describe glucose rate of appearance after meals [14]; b) a better exploitation of NNs strengths by using a NN to predict the components of the CGM signals which result not modelable though a simple linear approach such as poly(1).

The performance of the new prediction algorithm was tested on 5 virtual patients generated in silico via a Type 1 Diabetes simulator [11] and on one real patient. Results were shown to be better than those obtained, on the same data, by two previously published methods (i.e. [9] and [5]).

Future developments include a more exhaustive test of the new algorithm, and its comparison with other state of the art methods, on enlarged simulated and real datasets. Moreover, the possibility of exploiting information on injected insulin doses, when available, will be also investigated.

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