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Glycemic Trend Prediction Using Empirical Model Identification

Marzia Cescon and Rolf Johansson

Abstract— **Using methods of system identification and pre-diction, we investigate near-future prediction of individual-specific T1DM blood glucose dynamics with the purpose of a decision-making tool development in diabetes treatment. Two strategies were approached: Firstly, Kalman estimators based on identified state-space models were designed; Secondly, direct identification of ARX- and ARMAX-based predictors was done. Predictions over 30 minutes look-ahead were capable to track glucose variation even in sensible ranges for estimation data, but not on validation data.**

I. INTRODUCTION

Diabetes Mellitus is a chronic disease of disordered glucose metabolism due to defects in either insulin secretion from the pancreatic β-cells or insulin action. Type-1 diabetes (T1DM), also called insulin-dependent diabetes mellitus (IDDM) is characterized by no production of insulin what so ever, whereas type-2 diabetes is caused by decreased sensitivity of the tissues to the metabolic effect of insulin. The basic effect of insulin lack or insulin resistance is to prevent the efficient uptake and utilization of glucose by most cells of the body, resulting in abnormally high blood sugar levels (hyperglycemia). Sustained hyperglycemia is associated with acute ketoacidosis, nephropaty, rethinopaty, neuropathy and damages to the cardio-vascular system [1], therefore intensive insulin therapy aiming at near-normoglycemia (80-100 mg/dL) has been strongly promoted during the last decade, following the results of the major Diabetes Control and Complications Trial (DCCT) [2] and follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) [3] studies. Focusing on tight blood glucose targets, the strategy comprises test of blood glucose levels at least four times a day, taking insulin at least three times a day by injections or using a pump and patient assistance by health care team through visits and phone calls. Meanwhile, the lack of improved quality of life and above all, the occurence of induced hypoglycemic events which may result in seizure, coma and eventually death preclude the feasibility of such a DCCT-like intensive therapy.

Diabetes treatment still strongly depends on patient daily decisions and is mainly based upon empirical experience, a major challenge being the need of adapting insulin regimens, food intake and exercise to keep the glycemia within limits during daily life activities. In practice, most patients are rather conservative in order to prevent hypoglycemia, but remain far from the optimal treatment. Hence, the development of a prediction engine capable of personalized on-the-spot decision making concerning the most adequate choice of
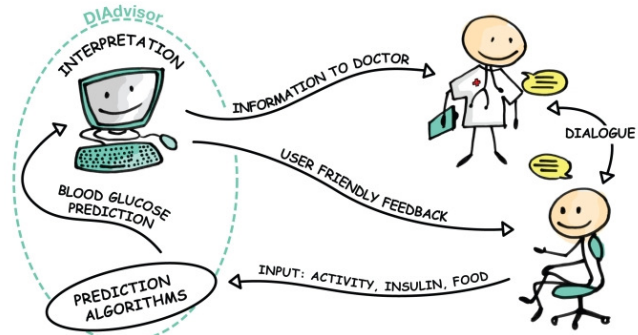
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Fig. 1. DIAdvisor modeling and prediction [12]

insulin delivery, meal intake and exercise would be a valuable initiative.

Currently, continuous glucose monitoring (CGM) devices are the available technology able to provide high/low glucose alarms when certain preset threshold levels have been crossed and to deliver early-warnings of events that are likely to occur if the current trend continues. To date many studies have investigated the possibility of predicting blood glucose concentration for the purpose of regulating glucose intervention, most of this research being based on data generated by a simulation model (e.g. [4], [5], [6], [7]). Originally developed by [8] the idea of T1DM CGM time-series analysis has been further pursued by [9] and [10] to predict near-future glucose concentration from its past history. However, the limited accuracy and the lack of exploitation of the dynamic interplay between previously injected insulin, meal intake and eventually exercise reduce or even eliminate the clinical benefits of the approach.

Purpose of this paper is to expand on [11] and investigate individual-specific predictive models from T1DM patient records. Two strategies were approached: Firstly, Kalman estimators based on identified state-space models were designed; Secondly, direct least-squares identification of various order ARX- and ARMAX-based predictors was done.

The organization of the paper is as follows. Section II presents the experimental data collection, the system modelling and prediction and the metrics used for predictors evaluation. Section III covers the findings and main contributions of the paper. Comments on the procedure adopted as well as the results achieved are touched upon in Sec. IV. Finally, Sec. V concludes the paper.
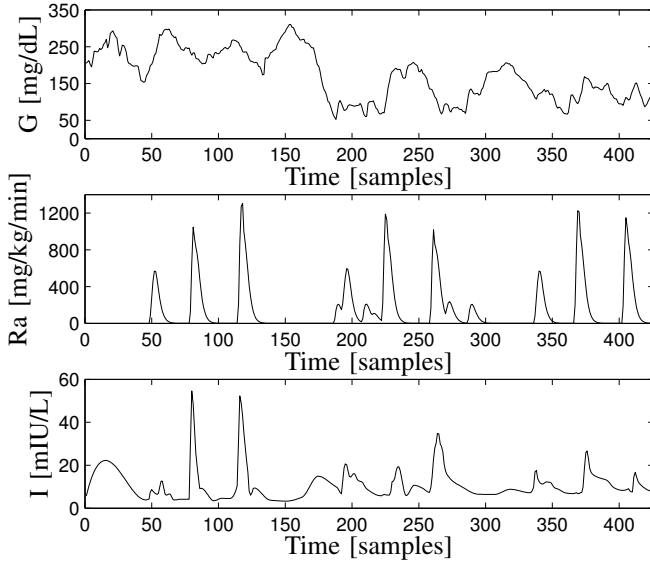
Fig. 2. Patient data used for estimation: glucose profile measured by CGMS (upper), glucose rate of appearance in plasma (middle), plasma insulin (lower). Notice extra carbohydrates intake to cope with consecutive hypoglycemic episodes for t = 180:300

II. METHODS

A. Data

In the framework of DIAdvisor^{TM}, a European FP7-IST research project on diabetic blood-glucose prediction and improved blood-glucose management in patients (Fig 1), acquisition of clinical diabetes data was accomplished in a series of experiment sessions [12]. Due to ongoing study at the time of manuscript preparation only one patient records gathered during three days of hospitalization in the Clinical Investigation Center participating in the DIAdvisor^{TM} Consortium were available. Collected data include: specific patient anthropological parameters (i.e., gender = male, age = 43 years old, BMI = 23.7, weight = 67 kg), characteristics related to diabetes (i.e., disease duration = 10 years, insulin delivery = external-pump), associated health conditions and therapies, food intakes registered in a logbook, blood glucose variations and plasma insulin profiles due to insulin therapy. Abbott FreeStyle Navigator [13] was used as Continuous Glucose Monitoring System (CGMS) for this study. Using amperometry, the sensor utilizes a working electrode coated with a sensing element that converts glucose concentration to electrical current. The system measures glucose levels once per minute and sends glucose information wirelessly to the pager-sized receiver once every 10 minutes. To begin data collection on Day 0 with a well-calibrated device, this sensor was inserted in the patient skin by a nurse 48 hours before the in-hospitalization. Calibrations against capillary blood glucose values obtained with the HemoCue glucose meter [14] were completed, as required by the Navigator system. During the whole stay at the clinic, the patient kept his current insulin therapy adjusting the boluses on his pump by himself on the basis of the HemoCue outcomes. Standard

meals for breakfast (8:00), lunch (13:00) and dinner (19:00) were served to the subject, the amount of administered carbohydrates being 42, 70 and 70 grams, respectively. Table I presents the schedule followed. Extra carbohydrates

TABLE I
MEALS AND BOLUSES SCHEDULE

Day	Meal time	Insulin bolus time
1	08.00	08.00
	13.00	12.55
	19.00	19.00
2	08.00	08.00
	13.00	13.45
	19.00	19.00
3	08.00	08.00
	13.00	14.00
	19.00	20.15

Notice the splits between meal time and insulin injections in Day 2 and 3 to separate the effects of the inputs.

were administered to the patient in day 2 due to repeated hypoglycemic episodes. Blood samples were collected by nurses to measure blood glucose and insulin (free and total) concentrations: every hour during day, every 2 hours during night, every 15 minutes after meals for 2 hours. Specific sampling schedule was adopted after breakfasts: 30 min before, mealtime, 10, 20, 30, 60, 90, 120, 150, 180, 240, 300 min after.

B. Input modeling

Inputs to the model are the appearance of glucose in plasma resulting from a meal and blood total insulin concentration. In order to obtain the rate of appearance of glucose in the blood after a meal the physiological model of glucose intestinal absorption first presented in [15] was adopted. It relies on a three-compartment model described as follows:

$$\begin{cases} \dot{q}_{sto1}(t) = -k_{21} \cdot q_{sto1}(t) + D \cdot \delta(t) \\ \dot{q}_{sto2}(t) = -k_{empt} \cdot q_{sto2}(t) + k_{21} \cdot q_{sto1}(t) \\ \dot{q}_{gut}(t) = -k_{abs} \cdot q_{gut}(t) + k_{empt} \cdot q_{sto2}(t) \\ Ra(t) = \frac{f \cdot k_{abs} \cdot q_{gut}(t)}{m_{BW}} \end{cases} \quad (1)$$

where q_{sto1} [mg] and q_{sto2} [mg] are the amounts of carbohydrates in the stomach (solid and liquid phase, respectively), D [mg] is the amount of ingested carbohydrates, q_{gut} [mg] is the carbohydrate mass in the intestine, k_{21} is the rate of grinding, k_{empt} the rate of gastric emptying, k_{abs} the rate of absorbtion, f the fraction of intestinal flux that actually appears in plasma, m_{BW} [kg] the body weight, k_{empt} the rate of gastric emptying according to:

$$\begin{aligned} k_{empt}(q_{sto}) = \quad & k_{min} + k + \{\tanh[\alpha(q_{sto} - b \cdot D)] \\ & - \tanh[\beta((q_{sto} - c \cdot D)] + 2\} \quad (2) \end{aligned}$$

$$k = \frac{k_{max} - k_{min}}{2}, \ \alpha = \frac{5}{2 \cdot D \cdot (1-b)}, \ \beta = \frac{5}{2 \cdot D \cdot c} \quad (3)$$

Ra [mg/kg/min] the rate of appearance of glucose in plasma and k_{max}, k_{min}, b, c are parameters as outlined in [15]. In this paper, given the impossibility of identifying and

consequently adapting the above mentioned parameters to the subject due to lack of data, mean population parameters values were considered, as introduced in [11].

As far as the insulin is concerned, despite the fact that there are quite well-known models for insulin dynamics in the literature [16], [17], no modeling for subcutaneous insulin absorption was embraced. Indeed, exploitation of the subject data records made it possible to use the insulin blood total concentration measured in hospital. Originally non-uniformly sampled, the insulin signal was linearly interpolated and uniformly resampled, the resampling period of the system being 10 minutes.

C. Empirical models and predictors

Aim of the work is to develop optimal τ-steps-ahead predictions of blood glucose evolution based on clinical experiments, the problem being tackled according to two different strategies: first, computing a Kalman predictor based on a previously identified state-space input-output model; secondly, preoceeding with direct low order *ARX*- and *ARMAX*-based predictor identification. Hence, denoting with $u_k \in \mathbb{R}^2$ glucose and insulin in the blood stream, $y_k \in \mathbb{R}$ plasma glucose concentration and $e_k \in \mathbb{R}$ the innovation process, i.e., the one-step-ahead prediction error, state space innovation models of the form

$$\begin{cases} x_{k+1} = Ax_k + Bu_k + Ke_k \\ y_k = Cx_k + e_k \end{cases} \quad (4)$$

shall be identified from T1DM patient data. Furthermore, since $e_k = y_k - \hat{y}_k$, reconstructing the innovation sequence e_k from the observation sequence y_k the state-space of the output predictor $\hat{y}_k$ based on the past joint data may be written:

$$\begin{cases} x_{k+1} = (A - KC)x_k + Bu_k + Ky_k \\ \hat{y}_{k|k-1} = Cx_k \end{cases} \quad (5)$$

It is a well-known fact that 4 and 5 have the same state-space, making the predictor realization a more general framework for subspace identification [18]. Throughout this work, the *n4sid* routine and the recently proposed *PBSID$_{opt}$* algorithm [19] based on predictor identification were compared.

Secondly, consider an ARMAX model in the following form:

$$A(z^{-1})y_k = B(z^{-1})u_k + C(z^{-1})w_k \quad (6)$$

where

$$\begin{array}{rcl} A(z^{-1}) &=& 1 + a_1 z^{-1} + \cdots + a_{n_a} z^{-n_a} \quad (7) \\ B(z^{-1}) &=& b_1 z^{-1} + \cdots + b_{n_b} z^{-n_b} \quad (8) \\ C(z^{-1}) &=& 1 + c_1 z^{-1} + \cdots + c_{n_c} z^{-n_c} \quad (9) \end{array}$$

u_k, y_k as above and w_k denotes the coloured noise. By expanding the *C*-polynomial according to the Diophantine equation

$$C(z^{-1}) = A(z^{-1})F(z^{-1}) + z^{-\tau}G(z^{-1}) \quad (10)$$

with τ accounting also for the relative input-output delay, we have

$$y_{k+\tau} = F(z^{-1})w_{k+\tau} + \frac{B(z^{-1})F(z^{-1})}{C(z^{-1})}u_k + \frac{G(z^{-1})}{C(z^{-1})}y_k \quad (11)$$

where the first term depends on future noise components only, the second and third term on data up to time k. Solving for $\{w_k\}$ from input-output data, the τ-step-ahead prediction results to be given by the conditional expectation of $y_{k+\tau}$ based on data up to time k:

$$\hat{y}_{k+\tau|k} = \mathcal{E}\{y_{k+\tau|k}\} = \frac{B(z^{-1})F(z^{-1})}{C(z^{-1})}u_k + \frac{G(z^{-1})}{C(z^{-1})}y_k \quad (12)$$

By means of parameter estimation it is possible to determine the parameter vector minimizing the sum of squared prediction errors:

$$\begin{array}{rcl} \hat{y}_{k+\tau|k} &=& -\alpha_1 \hat{y}_{k+\tau-1|k-1} - \cdots - \alpha_{n_\alpha} \hat{y}_{k+\tau-n_\alpha|k-n_\alpha} \quad (13) \\ && +\beta_0 u_k + \cdots + \beta_{n_\beta} u_{k-n_\beta} + \quad (14) \\ && +\gamma_0 y_k + \cdots + \gamma_{n_\gamma} y_{k-n_\gamma} \quad (15) \end{array}$$

The following relationships hold:

$$\begin{array}{rcl} \alpha(z^{-1}) &=& C(z^{-1}) \quad (16) \\ \beta(z^{-1}) &=& B(z^{-1})F(z^{-1}) \quad (17) \\ \gamma(z^{-1}) &=& G(z^{-1}) \quad (18) \end{array}$$

with compatible polynomial degrees: $n_\alpha = n_C$, $n_\beta = n_B + n_F$, $n_\gamma = n_G$.

Our methodology consisted in estimating ARX-based predictors (i.e., when $\alpha(z^{-1}) = C(z^{-1}) = 1$) of various orders and then building on this with pseudo-linear regression strategy to obtain the polynomial parameters of $\alpha(z^{-1})$.

D. Prediction evaluation

The quality of the predictors developed was assessed by statistical model validation and mathematical metrics in order to quantify the error between the predicted profile vs. the original one and diabetes-specific metrics to show their impact in terms of clinically-relevant detected events. Thus, the predicted profile precision was evaluated with respect to the following:

- Percentage FIT
- Percentage Variance Accounted For (VAF)
- Root Mean Squared Error (RMSE) $[mg/dL]$

The clinical accuracy of the predictions was evaluated in terms of both correctness of predicted glucose values and ability to capture the direction and rate of change of glucose fluctuations by the continuous glucose-error grid analysis (CG-EGA) which comprises a point-error grid and a dynamic rate-of-change error grid [20]. In both of them each prediction-measured value pair is assigned to one of A-E labeled zones. Points falling into Zone A are considered clinically accurate; points in Zone B are benignly erroneous; points in Zone C may lead to an overcorrected treatment whereas point in Zone D may lead to undercorrected measures. Last, points in Zone E are highly erroneous.

III. RESULTS

As far as the entire three-days data sequence is concerned, state-space models of fifth order were selected according to the most significant singular values and have been subsequently used in a Kalman filter for prediction, their predictive capabilities being compared with first order *ARX*- and second order *ARMAX*-based predictors. Table II offers a quantitative assessment of 30, 60, 90, 120 minutes ahead predictions on estimation data achieved with the above mentioned approaches. The superiority of the state-space model-based predictor identification strategy appears clearly over all the prediction horizons. The most significant achievement is a root-mean-squared error of 17.06 $[mg/dL]$ on the short 30 minutes look ahead by $PBSID_{opt}$. In order to assess delays, the table reports the zero-order-hold (*ZOH*) for comparison. It is, indeed, important for alert generation to detect changes with a delay smaller than the prediction horizon. Table III is concerned with the point error grid analysis for the evaluation of prediction performances over 30 minutes prediction horizon on calibration data. State-space model-based predictions exhibit the best performances. Notice the bigger accuracy obtained in comparison to what achieved by projecting the last value with a *ZOH*.

In a second phase the data was, then, randomly splitted into two parts: one for estimation and the other for validation. Model order was fixed to 2. Figure 4 shows for prediction horizons of 30 minutes, the real (dotted line) versus the predicted (solid line) glucose curve for state-space model-based predictors: *n4sid* (top left) and $PBSID_{opt}$ (top right); and direct identification of *ARX*- (bottom left) and *ARMAX*-based predictors (bottom right) on validation data. From a qualitative point of view, Fig.4 suggests that none of the approaches is clearly superior to the other. Nevertheless, the predictor-based subspace identification strategy, namely $PBSID_{opt}$, seems to outperform the other methods, being more prompt in tracking ascending as well as descending trends with clinically tolerable delays. However, in order for the approach to be consider useful in practice, wrong forecasts leading to the generation of false hypo- and hyperglycemic alarms need to be avoided. In the case examined, such an event is visible at $t = 65$ with an unacceptable mismatch of $75[mg/dL]$. Figure III quantifies the accuracy of validation data prediction by means of the continuous glucose-error grid analysis in the case of the *ARMAX*-based predictor. The grid on the left shows that 82% points fell into the A zone and 16.5% into the B zone. Dynamic characteristics of the prediction, namely the rate-of-change accuracy, are shown in Fig. III right grid.

IV. DISCUSSION

Over the last decades, a wealth of models describing the insulin-to-glucose system dynamics was developed for the purpose of simulation and glycemic control, the approach being physiology based [6], [5], [21]. Very recently the problem of identifying such a model has been tackled from a data-driven perspective mainly using simulated data from model in the literature [22], [23]. Indeed, fitting actual T1DM

TABLE III

EVALUATION OF PREDICTOR PERFORMANCES ON 30 MIN PREDICTION HORIZON

Predictor	zone A	zone B	zone C	zone D	zone E
n4sid	88.0282	10.7981	0	1.1737	0
$PBSID_{opt}$	87.0892	10.5634	0	2.3474	0
ARX	77.9621	20.3791	0	0.9524	0
ARMAX	86.1905	12.6190	0	1.6588	0
ZOH	82.8638	14.0845	0	2.3474	0.7042

Percentage of point falling within regions. Fifth order *n4sid* and $PBSID_{opt}$ based models ; first order *ARX* and second order *ARMAX*.

subject data to the models has been treated to a much less extent (e.g., [11], [24], [25], [26]) given the difficulties in gathering appropriate patient records.

This paper dealt with a unique dataset which is being collected [12] and looks promising for future exploitation.

As far as meal modeling is concerned, the proposed strategy in [11] seems to be a theoretically sound attempt to account for differences in meal compositions. However, it was not possible to apply it in this context due to unavailable meal composition information. Moreover, the adaptation of parameter values of the physiological model representing gut absorption to the specific subjects could lead to better estimates of the overall dynamic model.

The use of subspace-based algorithms for identification of linear-time-invariant systems was investigated, the reason being these methods do not require parameterization of the model class, are non-iterative and numerically robust; moreover, they have been proven to be suitable in identifying MIMO systems. Among those, a new class of methods based on identification of a predictor model in a prediction error method (PEM) fashion was considered [18]. In particular, the $PBSID_{opt}$ algorithm in [19] was used. This algorithm requires the choice of three parameters by the user: the model order *n*, the length of the past horizon *p* and the length of the future horizon *f*. In particular, it is not clear how the future horizon affects the quality of the estimation, albeit it has been shown that its optimal choice can lead to better estimates [27]. Hence, parameter values were decided in a trial-and-error manner. It was empirically noticed, however, that decreasing the future horizon worsens the estimation, increasing the past horizon improves up to a limit. As for the model order, the selection was made on the basis of the singular values of the system. Model order $n = 5$ appeared to describe the input-output behaviour sufficiently well. However, for validation data the model order was chosen smaller than the prediction steps.

In addition to model-based predictors, direct predictor identification was pursued, given its relevance in contexts where models are poor or not available.

In order to assess robustness of the proposed models for prediction, population studies and cross validation over different subjects are needed. Moreover, further improvements of the state-of-the-art in identification, e.g., the ability of handling non-uniformly sampled data, reduction of sensitivity to initial conditions and automatic selections of model
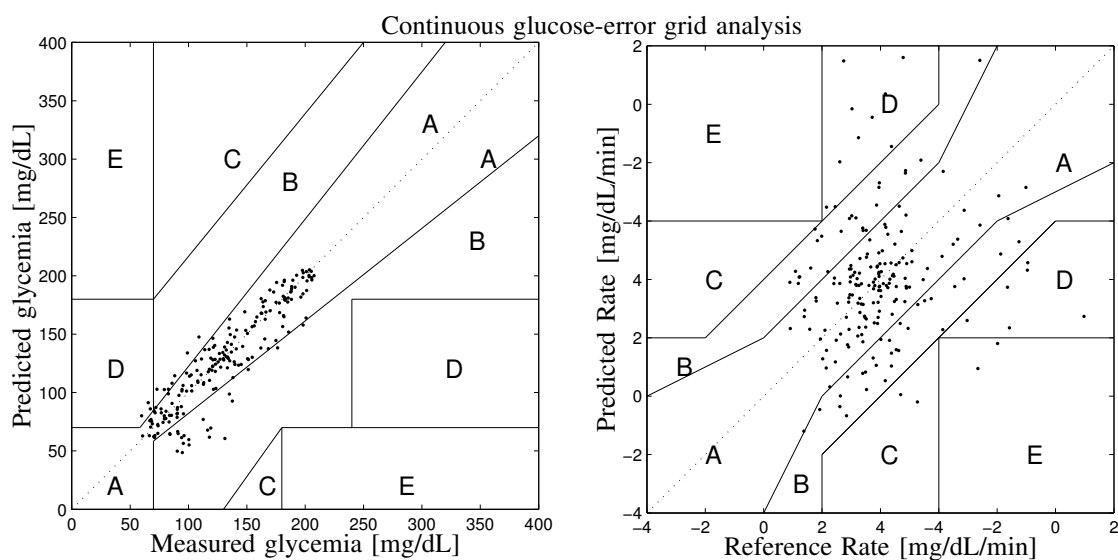
Fig. 3. Continuous glucose error grid analysis: CGMS-measured glycemia vs Predicted glycemia in pEGA (left); Measured rate vs Predicted rate in rEGA (right). Glucose was predicted 30 min ahead in time with second order *ARMAX*-based predictor. Notice that the prediction considers data saved for validation.
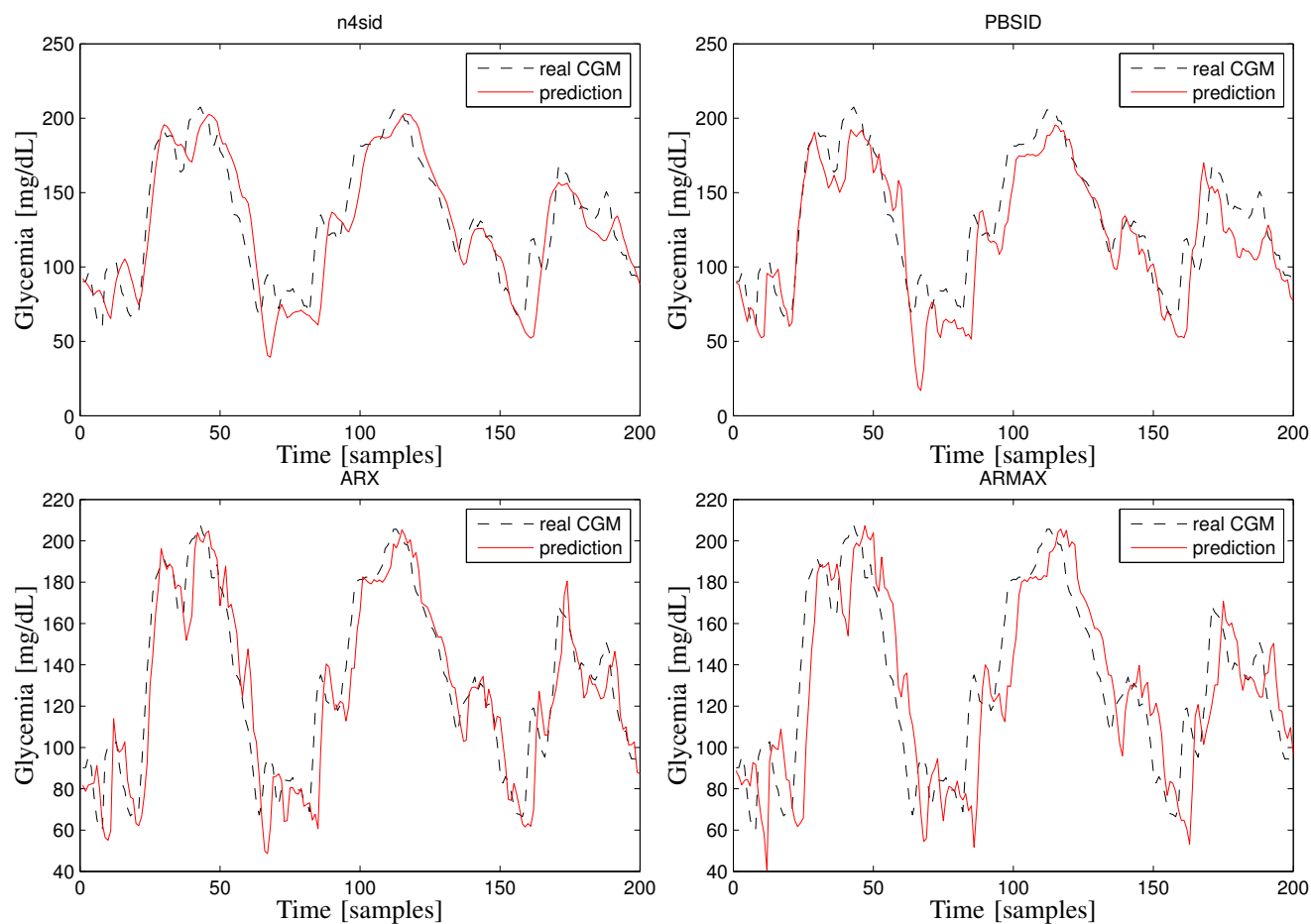

Fig. 4. 30 minutes ahead prediction of data saved for validation: measured glycemia (dotted black) compared to predicted glycemia (solid red). Notice that the model order for all the model was chosen to be 2.

TABLE II

Evaluation of predictor performances over prediction horizons of 30, 60, 90, 120 minutes using estimation data

Predictor	30min			60min			90min			120min		
	FIT	VAF	RMSE	FIT	VAF	RMSE	FIT	VAF	RMSE	FIT	VAF	RMSE
$n4sid$	73.78	93.12	17.72	61.92	85.50	25.73	54.38	79.19	30.83	47.02	71.93	35.81
$PBSID_{opt}$	74.75	93.70	17.06	63.50	87.01	24.67	57.11	82.36	28.98	51.34	77.54	32.89
ARX	61.03	87.19	26.42	38.39	76.28	41.86	15.36	53.96	59.56	5.26	18.71	78.33
$ARMAX$	72.28	92.49	18.82	55.45	80.88	35.28	50.16	75.22	54.48	27.72	67.21	61.39
ZOH	59.67	84.41	27.26	41.55	63.15	41.06	26.26	39.41	52.64	13.40	13.53	62.93

fifth-order $n4sid-$ and $PBSID_{opt}$-based predictors; second-order ARX- and $ARMAX$-based predictors.

parameters, would be valuable.

V. CONCLUSIONS

The present contribution was concerned with short-term model-based prediction of blood glucose evolution. Prediction results for a representative T1DM patient were shown. Predictors showed capability of predicting hance allowing for preventing both hypoglycemic and hyperglycemic events with a prediction horizon of 30 minutes with a root mean squared error of 17.06 $[mg/dL]$ on calibration data and of 18.08 $[mg/dL]$ on validation data. However, consistency and robustness of the proposed approach across different subjects was not demonstrated and is, thus, left for future work.

VI. AKNOWLEDGMENT

REFERENCES

[1] G. Williams and J. C. Pickup, *Handbook of Diabetes*, Blackwell Science, Ed. MSD, 1999.

[2] The Diabetes Control and Complications Trial Research Group, "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus," *N Eng J Med*, vol. 329, no. 14, pp. 977–986, September 1993.

[3] The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group, "Intensive diabetes treatment and cardiovascular disease in patients with rype 1 diabetes," *N Eng J Med*, vol. 353, no. 25, pp. 2643–2653, December 2005.

[4] R. Hovorka, V. Canonico, L. J. Chassin, U. Haueter, M. Massi-Benedetti, M. Orsini Federici, T. R. Pieber, H. C. Schaller, L. Schaupp, T. Vering, and M. E. Wilinska, "Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes," *Physiological Measurement*, vol. 25, pp. 905–920, 2004.

[5] A. Roy and R. S. Parker, "Dynamic modeling of free fatty acid, glucose, and insulin: An extended "minimal model"," *Diabetes Technology and Therapeutics*, vol. 8, no. 6, pp. 617–626, 2006.

[6] C. Dalla Man, R. A. Rizza, and C. Cobelli, "Meal simulation model of the glucose-insulin system," *IEEE Trans. Biomedical Eng.*, vol. 54, no. 10, pp. 1740–1749, October 2007.

[7] M. W. Percival, W. C. Bevier, H. Zisser, L. Jovanovic, D. E. Seborg, and F. J. D. III, "Prediction of dynamic glycemic trends using optimal state estimation," in *Proc. 17th IFAC World Congress*, Seoul, Korea, July 2008.

[8] T. Bremer and D. A. Gough, "Is blood glucose predictable from previous values? a solicitation for data," *Diabetes*, vol. 48, pp. 445–451, March 1999.

[9] G. Sparacino, F. Zanderigo, S. Corazza, A. Maran, A. Facchinetti, and C. Cobelli, "Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series," *IEEE Trans. Biomedical Eng.*, vol. 54, no. 5, pp. 931–937, May 2007.

[10] A. Gani, A. V. Gribok, S. Rajaraman, W. K. Ward, and J. Reifman, "Predicting subcutaneous glucose concentration in humans: Data-driven glucose modeling," *IEEE Trans. Biomedical Eng.*, vol. 56, no. 2, pp. 246–254, February 2009.

[11] M. Cescon, F. Ståhl, M. Landin-Olsson, and R. Johansson, "Subspace-based model identification of diabetic blood glucose dynamics," in *Proc. 15th IFAC Symposium on System Identification*, Saint Malo, France, July 2009.

[12] DIAdvisor www.diadvisor.eu.

[13] Abbott Diabetes Care www.abbottdiabetescare.com.

[14] HemoCue www.hemocue.com.

[15] C. Dalla Man, M. Camilleri, and C. Cobelli, "A system model of oral glucose absorption: Validation on gold standard data," *IEEE Trans. Biomedical Eng.*, vol. 53, no. 12, pp. 2472–2477, December 2006.

[16] G. Nucci and C. Cobelli, "Models of subcutaneous insulin kinetics. a critical review," *Computer Methods and Programs in Biomedicine*, vol. 62, pp. 249–257, 2000.

[17] M. E. Wilinska, L. J. Chassin, H. C.Schaller, L. Schaupp, T. R. Pieber, and R. Hovorka, "Insulin kinetics in type-1 diabetes: Continuous and bolus delivery of rapid acting insulin," *IEEE Trans. Biomedical Eng.*, vol. 52, no. 1, pp. 3–12, January 2005.

[18] A. Chiuso and G. Picci, "Prediction error vs subspace methods in closed-loop identification," in *Proc. 16th IFAC World Congress*, Prague, Czech Republic, July 2005.

[19] A. Chiuso, "The role of vector autoregressive modeling in subspace identification," *Automatica*, vol. 43, no. 6, pp. 1034–1048, June 2007.

[20] B. Kovatchev, D. Cox, L. Gonder-Frederick, and W. Clarke, "Evaluating the accuracy of continuous glucose-monitoring sensors," *Diabetes Care*, vol. 27, no. 8, pp. 1922–1928, august 2004.

[21] A. Makroglou, J. Li, and Y. Kuang, "Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview," *Applied Numerical Mathematics*, vol. 56, pp. 559–573, 2006.

[22] C. Palerm, M. Rodriguez-Fernandez, W. C. Bevier, H. Zisser, J. R. Banga, L. Jovanovic, and F. J. D. III, "Robust parameter estimation in a model for glucose kinetics in type 1 diabetes subjects," in *Proc. 28th IEEE EMBS Ann. Int.Conf.*, New York City, USA, August 2006.

[23] D. A. Finan, H. Zisser, L. Jovanovic, W. C. Bevier, and D. E. Seborg, "Identification of linear dynamic models for type 1 diabetes: a simulation study," in *Proc. IFAC*, 2006.

[24] F. Ståhl and R. Johansson, "Short-term diabetes blood glucose prediction based on blood glucose measurements," in *Proc. 30th IEEE EMBS Ann.Int.Conf. (EMBC2008)*, Vancouver, BC, Canada, August 2008, pp. 292–294.

[25] ——, "Diabetes mellitus modeling and short-term prediction based on blood glucose measurements," *Mathematical Biosciences*, vol. 217, pp. 101–117, 2009.

[26] D. A. Finan, C. C. Palerm, F. J. D. III, H. Zisser, L. Jovanovic, W. C. Bevier, and D. E. Seborg, "Identification of empirical dynamic models for type 1 diabetes subject data," in *Proc. American Control Conference (ACC2008)*, Seattle, WA, USA, 2008.

[27] A. Chiuso, "Choosing the future horizon in closed-loop cca-type subspace algorithms," *Automatica*, vol. 30, pp. 75–93, 2008.

[28] R. Johansson, *System Modeling and Identification*. Englewood Cliffs, NJ: Prentice Hall, 1993.

[29] P. Van Overschee and B. de Moore, "N4SID: Subspace algorithms for the identification of combined deterministic-stochastic systems." *Automatica*, vol. 30, pp. 75–93, 1994.