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Adaptive Subspace-based prediction of T1DM glycemia

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Abstract— **Blood glucose levels fluctuate widely in Type 1 diabetic patients expecially during stressful situations, intercurrent illness, exercise and changes in meal composition. Furthermore, inter- and intra-subject variability make the prediction of such fluctuations an even harder task. The paper deals with the application of online data-driven multi-step subspace-based patient-specific predictor models to T1DM glycemia prediction, exploiting the interplay between previously injected insulin, meal intake and eventually vital signs. When the unknown underlying model is changing over time we believe such an adaptive scheme may constitute a valuable step towards the development of an advisory tool capable of informing the patient at any time about the evolution of glycemia and possibly give advices on the most appropriate control action to take [1].**

I. INTRODUCTION

Diabetes Mellitus is a disease characterized by a chronically raised blood glucose concentration due to impaired carbohydrates, proteins and fats metabolism caused by defects in either insulin secretion from the pancreatic β-cells or insulin action [2]. In particular, type 1 diabetes mellitus (T1DM), target of this contribution, is characterized by no production of insulin whatsoever. The complications of the disease can be costly to the health care system and devastating to the patient. For this reason, it is critical for diabetes patients to regulate their blood glucose tightly. Because insulin deficiency defines T1DM, exogenous insulin replacement is the hallmark of the therapy. In the non-diabetic subjects, insulin is secreted into the portal circulation at a low basal rate throughout the 24 hours superimposed with an augmented secretion during meals. Hence, the idea behind conventional therapy insulin regimens is to mimic with subcutaneous injections this secretion pattern. Many factors influence glycemia such as changes in diet, physical activity, stress or intercurrent illness and therefore insulin requirements are never fixed. Adjusting their own insulin dosing in response to high or low glucose levels at particular times of the day represents the toughest challenge for the diabetic patients. The availability of prediction models capable of estimating the expected blood glucose profile in the near future during daily life would clearly support them in the non-trivial decision making task.

Recent years' advances in self-monitoring devices have made frequent (e.g., every 5-10 minutes) and well-sampled glucose concentration data readily available for several days, opening to new possibilities in diabetes management. Most of the continuous glucose meters (CGM) are minimally invasive, assessing glucose concentration indirectly via interstitial fluid sampling from the subcutaneous tissues, e.g., [3].

To date many studies have developed empirical models from type 1 diabetes data in order to predict future blood glucose trajectories. Originally developed by [4] the idea of T1DM CGM time-series analysis has been further pursued by [5] and [6] to predict future glucose concentration from its past history. However, none of these works considered the dynamic interplay between previously injected insulin, meal intake and eventually exercise. Attempts at including in the prediction model insulin and carbohydrates can be found in [7], [8], [9], [10], [11] and [12]. A different approach is that of [13] and [14] focusing on insulin sensitivity prediction and consequently on the resulting blood glucose prediction by means of stochastic models for critically ill patients. Nevertheless, a peculiarity of diabetic subjects blood glucose dynamics is that it heavily varies over time, often quickly and unexpectedly. As a consequence, a linear-time-invariant model may not be sufficient to produce accurate forecasts of future glycemia [12]. In addition, a sound and valid patient-specific dynamical model of the glucose metabolism is still unavailable, despite extensive research [15].

That said, the purpose of this article is to present on-line data-driven multi-step ahead predictions of T1DM patients blood glucose levels, exploiting meal informations, insulin dosing and vital signs.

We shall be concerned with a recursive version of a class of subspace-based multi-step predictors presented in [16], [17], namely those based on the PBSID algorithm [18], [19]. We therefore refer the reader to the above mentioned works for a thorough discussion on the subject matter, suffices it here to review the basic steps only, adding the novelty represented by the updating scheme.

The remainder of the paper is organized as follows. Section II deals with the experimental conditions, the modeling strategy and the subspace-based recursive multi-step predictors derivation and implementation. Section III shows the main results divided into three subsections corresponding to different real-life situations. In Sec. IV comments on the procedure as well as remarks concerning the achievements are provided. Finally, Sec. V summarizes the findings and hints to future work.

II. METHODS

A. Experimental conditions

Data collection was accomplished in a major data acquisition trial taking place at the Centre d'Investigation Clinique de Montpellier, France, within DIAdvisor^{TM} [1],

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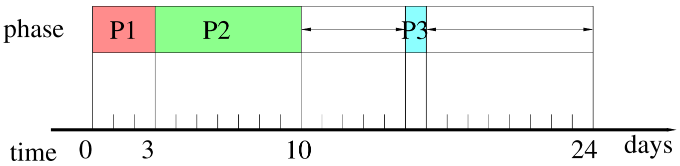

Fig. 1. Data Acquisition Schedule. Phase P1 corresponds to the in-hospital test from day 0 to day 3; phase P2 corresponds to the ambulatory test from end of day 3 to day 10 ± 2 ; phase P3 corresponds to the exercise test one day between end of day 10 and day 24

a large scale FP7 European project. Ethics approval for the collection and publication of data was obtained by the ethical committee of the investigation center. The study comprised three consecutive phases, namely, an in-hospital test, an ambulatory test and an exercise test, the data being collected over a window of 14 days in total according to the flow chart depicted in Fig. 1. No specific intervention on usual diabetes treatment was scheduled during the study since a faithful picture of blood glucose fluctuations and insulin-glucose interactions in various environmental conditions was pursued, the patients continuing adapting their insulin therapy based on the outcome of their own glucose meter and following standard physicians' recommendations. For the whole duration of the study the partecipants were equipped with the CGMS Abbott Freestyle Navigator® [3] and the VivoMetrics LifeShirt® [20] devices, making it possible to record interstitial glucose levels every 10 minutes, heart rate, respiration rate and body movements every minute and were asked to annotate in a personal logbook insulin types, doses and times of injections. During the first phase, the patients were served standardized meals for breakfast (8:00), lunch (13:00) and dinner (19:00), the amount of administered carbohydrates being 42, 70 and 70 grams, respectively, whereas in the ambulatory period, the subjects wrote on the logbook time and estimated carbohydrate content of their meal intakes. Finally, the specific exercise test, taking place at the hospital, consisted of a 30-minutes exercise bout 2 hours after a standardized 42 grams carbohydrates breakfast using an ergo-cyclometer, the effort being constant and above the anaerobic threshold. Figure 2 shows one such data series for a representative patient.

B. Modeling Strategy

The physiology of glucose metabolism in diabetes was considered having one output, i.e., glycemia, and two main inputs, i.e., carbohydrate intake and administered insulin [15]. Further, given that physical activity has been proven to decrease plasma glucose levels due to increased glucose uptake by the exercising muscles [2], the effects of exercise, i.e., increased heart rate, respiration rate and body movements, were therefore regarded as additional inputs. Physiological models from the literature [21] exploiting mean population parameter values were used to filter the raw informations on meals and insulin to obtain glucose rate of appearance in plasma after a carbohydrate intake and appearance of insulin in plasma after a dose. Sample period was 10 [min].

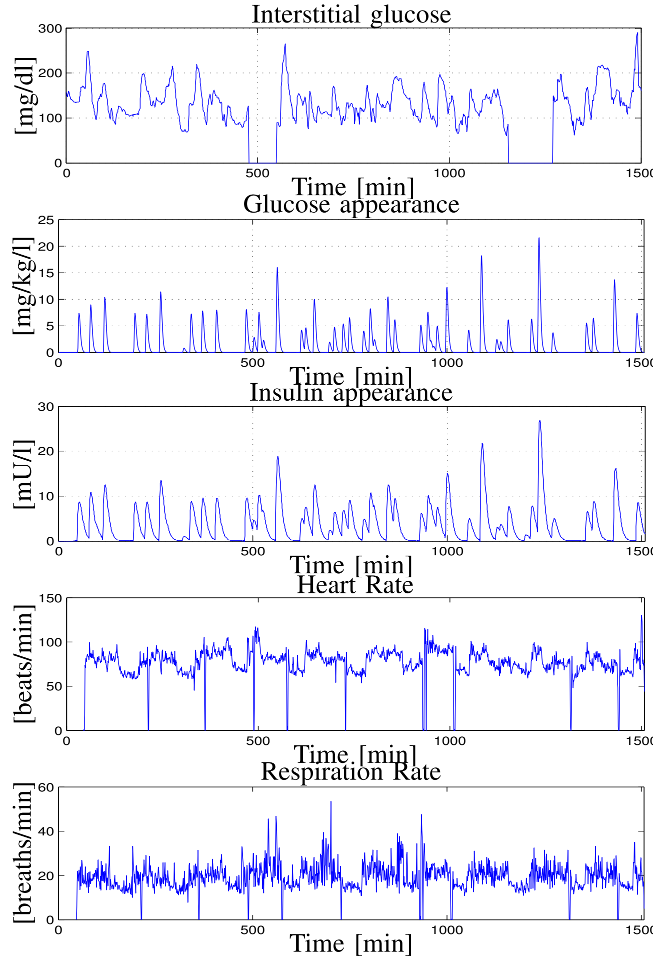

Fig. 2. Representative patient data. *Top* Interstitial glucose [mg/dl], *Top Center* Glucose rate of appearance in plasma [mg/kg/l], *Center* Insulin rate of appearance in plasma [mU/l]; *Top Bottom* Heart rate [beats/min], *Bottom* Respiration rate [breaths/min]. All the data vs. Time [min]

C. Online subspace-based multi-step predictors

Let a finite input sequence $\{u_k\}_{k=k_0}^{T+N}$ and the corresponding output sequence $\{y_k\}_{k=k_0}^{T+N}$ be generated by a discrete-time linear-time-invariant system $\Sigma_n(A,B,C,D,K)$ in innovation form

$$\begin{cases} x_{k+1} = Ax_k + Bu_k + Ke_k \\ y_k = Cx_k + Du_k + e_k \end{cases} \tag{1}$$

with input $u_k \in \mathbb{R}^m$, output $y_k \in \mathbb{R}^l$, state vector $x_k \in \mathbb{R}^n$ and zero-mean white noise innovation process, i.e., one-step ahead prediction error, $e_k = y_k - \hat{y}_k$. Let us define for future reference $\bar{A} = A - KC$ and denote the joint input-output process assumed to satisfy the condition of persistent excitation of sufficiently high order by $z_k = [u_k^T y_k^T]^T$. Further, without loss of generality, let us assume no direct feedthrough, i.e., $D = 0$.

Throughout the paper k shall denote the current time instant in the identification problem, k_0 shall be the initial time from which the data are collected, so that $k - k_0$ is the past horizon in the identification problem denoted by p, T shall be such that $T - k$ represents the future horizon denoted by f, while t shall be the sample index in the prediction problem, $t > T+N$. Finally, the number of steps in the look ahead will be denoted by τ.

The available data sequences $\{u_k\}$, $\{y_k\}$ and the innovation process $\{e_k\}$ will be organized in Hankel-type matrices denoted by uppercase letters, the subscript indexes standing for the argument of the upper left and lower left elements of the first column, respectively; accordingly, finite length process tails will be represented by the block rows of the block Hankel data matrices and denoted, with some abuse of notation, by uppercase letters with one subscript index only, e.g.,

$$Y_{[a,b]} := \begin{bmatrix} Y_a \\ Y_{a+1} \\ \vdots \\ Y_b \end{bmatrix} = \begin{bmatrix} y_a & y_{a+1} & \cdots & y_{a+N-1} \\ y_{a+1} & y_{a+2} & \cdots & y_{a+N} \\ \vdots & \cdots & \cdots & \vdots \\ y_b & y_{b+1} & \cdots & y_{b+N-1} \end{bmatrix}$$

Consider now (1) in predictor form:

$$\begin{cases} x_{k+1} = \bar{A}x_k + Bu_k + Ky_k \\ \hat{y}_{k|k-1} = Cx_k \end{cases} \tag{2}$$

Iterating the system equations to obtain the output tail at time $k+h$, $h \in [0,T)$:

$$Y_{k+h} = C\bar{A}^h X_k + \sum_{i=1}^{h} C\bar{A}^{h-i}(BU_{k+i-1} + KY_{k+i-1}) + E_{k+h} \tag{3}$$

and stacking all the data on top of each other, the following matrix relation can be written:

$$Y_{[k,T]} = \mathscr{O}X_{k_0} + \Xi Z_{[k_0,k)} + \Psi Z_{[k,T]} + E_{[k,T]} \tag{4}$$

where the first term depend on the initial conditions of the state, the second term depends upon past input-output data and the third on future input-output data. Matrices $\mathscr{O}$, Ψ and Ξ are given in (7) and (8). Discarding the effects of mishandled initial conditions for sufficiently large p (details in [18]), the Markov parameters of the system (1) can be found solving the least-squares problem:

$$Y_k = \Xi_0 Z_{[k_0,k)} + E_k \tag{5}$$

$$\hat{\Xi}_0 = \underset{\Xi_0}{\operatorname{argmin}} \; || \, Y_k - \Xi_0 Z_{[k_0,k)} \, ||_F^2 \tag{6}$$

where $||\cdot||_F$ stands for the Frobenius norm of a matrix. Using the estimated coefficients in $\hat{\Xi}_0$ and the recipe (9) with $1 \le i \le \tau$

$$\Gamma_i = \hat{\Xi}_i + \sum_{j=0}^{i-1} \hat{C}\hat{\bar{A}}^{i-j-1}\hat{K}\Gamma_j, \qquad \Gamma_0 = \hat{\Xi}_0 \tag{9}$$

the output predictors are given by [16], [17]:

$$\begin{bmatrix} \hat{Y}_{k+1|k} \\ \hat{Y}_{k+2|k} \\ \vdots \\ \hat{Y}_{k+\tau|k} \end{bmatrix} = \begin{bmatrix} \Gamma_1 \\ \Gamma_2 \\ \vdots \\ \Gamma_\tau \end{bmatrix} Z_{[k_0,k)} \tag{10}$$

D. Implementation details

The solution to the regression problem (6) can be obtained by factorization of $\begin{bmatrix} Z_{[k_0,k)} & Y_k \end{bmatrix}^T$ into a lower triangular matrix L and a matrix with orthogonal rows Q, i.e., the LQ decomposition:

$$\begin{bmatrix} Z_{[k_0,k)} \\ Y_k \end{bmatrix} = \underbrace{\begin{bmatrix} L_{11} & 0 \\ L_{21} & L_{22} \end{bmatrix}}_{L} \underbrace{\begin{bmatrix} Q_1^T \\ Q_2^T \end{bmatrix}}_{Q} \tag{11}$$

The sought parameters are then computed according to:

$$\hat{\Xi}_0 = L_{21}L_{11}^{-1} \tag{12}$$

Now, for an adaptive implementation, the predictor coefficients should be recomputed each time new data becomes available, i.e., each new time step. This is accomplished by solving (6) at every sampling instant by means of a "new", in the sense that it contains new data, LQ decomposition. Our approach moved from [22] and is based on the application of Givens QR Method [23] to calculate the factorization in (11) as follows. Let the blocks L_{11} and L_{21} at time $k-1$ be denoted by $L_{11}(k-1)$ and $L_{21}(k-1)$, respectively. When new input-output data are available at time k the vector $[z_p^T \quad y_k^T]^T$ can be appended to $[L_{11}(k-1)^T \quad L_{21}(k-1)^T]^T$; next, by applying a sequence of orthogonal Givens rotations $\mathscr{G}$ the matrix L' can be made lower triangular, i.e. updated, according to the following:

$$\underbrace{\left[\begin{array}{c|c} \sqrt{\lambda}L_{11}(k-1) & z_p \\ \hline \sqrt{\lambda}L_{21}(k-1) & y_k \end{array}\right]}_{L'} \mathscr{G} = \left[\begin{array}{c|c} L_{11}(k) & 0 \\ \hline L_{21}(k) & \tilde{y}_k \end{array}\right] \tag{13}$$

where a forgetting factor $\lambda \in [0.95, 1)$ may be used to discount old data. When $\hat{\Xi}_0$ containing the recursively estimated Markov parameters is found, the computation of the predictors is done as in the non-recursive case Eqs. (9), (10).

III. Results

In order to show how the proposed on-line predictors apply in the various situations we present results belonging to the three different phases of the data acquisition trial. We are interested in evaluating the performances on different prediction horizons τ, $1[min] \le \tau \le 30[min]$, with respect to the percentage Variance Accounted For (VAF):

$$\text{VAF} = 1 - \frac{var(\hat{y}_N - y_N)}{var(y_N)} \times 100$$

We use boxplots of the above mentioned metrics for multi look-ahead to display population results, where the central mark in each box is the median of the VAF over the population while the edges are the 25th and 75th percentiles, respectively.

In addition, we compare the results based on their qualitative behaviour, the prediction quality being not particularly crucial within the normoglycemia range, i.e. between $70-140$ [mg/dL] [24], but very important in detecting the trends and hypo-hyperglycemia excursions.

Throughout the simulations, user parameters were set to $\lambda = 0.98$, $p = f = 5$.

$$
\mathscr{O} = \begin{bmatrix} C \\ C\bar{A} \\ C\bar{A}^2 \\ \vdots \\ C\bar{A}^{T-1} \end{bmatrix}, \Psi = \begin{bmatrix} 0 & \cdots & \cdots & \cdots & \cdots & 0 \\ C[B \quad K] & 0 & \cdots & \cdots & \cdots & 0 \\ C\bar{A}[B \quad K] & C[B \quad K] & 0 & \cdots & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \ddots & 0 \\ C\bar{A}^{T-2}[B \quad K] & \cdots & \cdots & \cdots & C[B \quad K] & 0 \end{bmatrix}, \tag{7}
$$

$$
\Xi = \begin{bmatrix} \Xi_0 \\ \Xi_1 \\ \vdots \\ \Xi_T \end{bmatrix} = \begin{bmatrix} C\bar{A}^{p-1}[B \quad K] & C\bar{A}^{p-2}[B \quad K] & \cdots & \cdots & \cdots & C[B \quad K] \\ 0 & C\bar{A}^{p-1}[B \quad K] & \cdots & \cdots & \cdots & C\bar{A}[B \quad K] \\ \vdots & \ddots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & C\bar{A}^{p-1}[B \quad K] & \cdots & C\bar{A}^{T}[B \quad K] \end{bmatrix} \tag{8}
$$

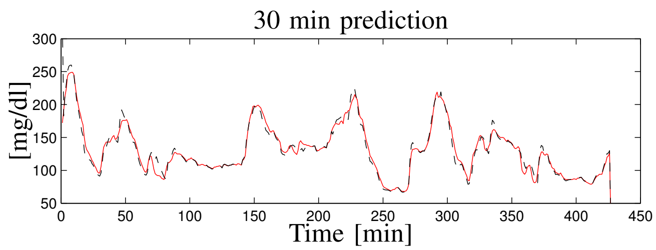

Fig. 3. Representative patient in hospital conditions. Predicted glucose profiles. CGMS measurements (red) vs. prediction obtained using glucose rate of appearance and insulin in plasma on a 30-minutes prediction horizon (dashed black)

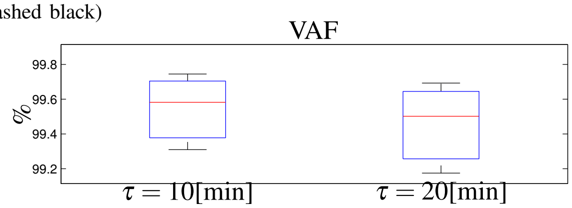

Fig. 4. Population study. Variance Accounted For. *Left* 10 min prediction, *Right* 20 min prediction. Each box presents results over the considered population. The central mark is the median, the edges of the box are the 25th and 75th percentiles.

A. In-hospital test

Data belonging to this phase were considered the most accurate, since the subjects were followed by research nurses and doctors in the hospital. Hence, insulin injections and standardized eaten meals could be used as input signals to the purpose of prediction. At the same time, physical activity was limited and therefore vital signs were not exploited for prediction. Figure 3 presents the predicted profiles of a representative patient during the in-hospital test. It is apparent how the proposed predictors can very well follow the real glucose profile on a short-term horizon.

Figure 4 refers to population results, showing the VAF for multi look-ahead $\tau = 10,\ 20$ [min].

B. Ambulatory test

We tested the predictors on three different scenarios:

- (data-rich case) Full data are available and no sensor failures occur

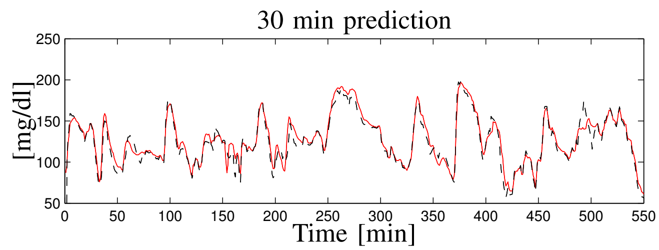

Fig. 5. Representative patient in ambulatory conditions. Data-rich case. Predicted glucose profiles. CGMS measurements (red) vs. prediction obtained with full data on a 30-minutes prediction horizon (dashed black)

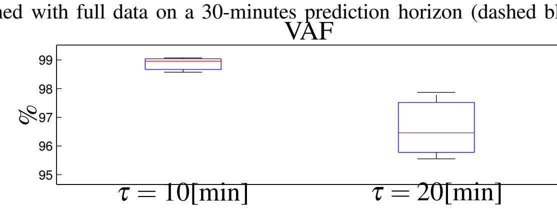

Fig. 6. Population study. Data-rich case. Variance Accounted For. *Left* 10 min prediction, *Right* 20 min prediction. Each box presents results over the considered population. The central mark is the median, the edges of the box are the 25th and 75th percentiles.

- (missing-meals case) The patient forgets to note one or more meals
- (no vital-signs available) The patient is not using the life vest

For the data-rich case, input to the predictors were glucose rate of appearance, insulin in plasma, heart rate and respiration rate. Figure 5 shows the predicted glucose profile for the representative patient. Figure 6 refers to population results, showing the Variance Accounted For for multi look-ahead $\tau = 10,\ 20$ [min].

During real life, estimating the carbohydrate content of a meal is prone to large errors. Moreover, the subjects often forget to write their meal intakes on the diary. In such a situation it may be helpful to rely upon insulin information and vital signs, possibly containing more informations than that during in-hospital low-activity level life, only. For this reason, we challenged the predictors accounting for insulin, heart rate and respiration rate. Figure 8 shows the predicted glucose profile for the same representative patient. Figure 9 refers to population results, showing the VAF for multi

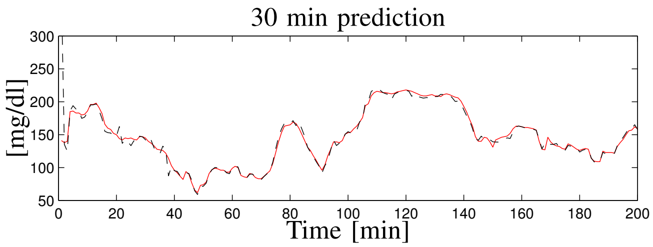

Fig. 7. Representative patient during exercise test. Predicted glucose profiles CGMS measurements (red) vs. prediction obtained using heart rate and respiration rate only (dashed black) on a 30-minutes ahead prediction

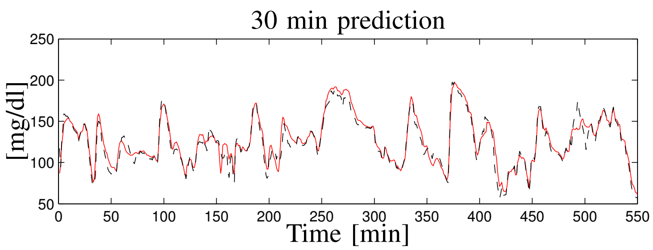

Fig. 8. Representative patient in ambulatory conditions. Missing- meals case. Predicted glucose profiles. CGMS measurements (red) vs. prediction obtained using insulin in plasma and vital signs on a 30-minutes prediction horizon (dashed black)

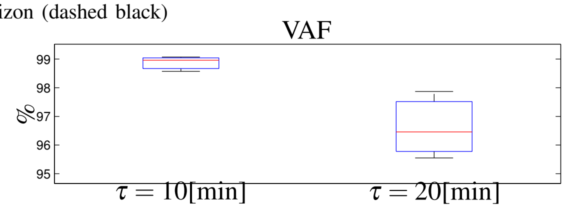

Fig. 9. Population study. Missing-meals case. Variance Accounted For. *Left* 10 min prediction, *Right* 20 min prediction. Each box presents results over the considered population. The central mark is the median, the edges of the box are the 25th and 75th percentiles.

look-ahead $\tau = 10$, 20 [min].

Finally, we assumed the life vest not to be available to the patients. Glucose rate of appearance in plasma and insulin in plasma were used only. Figure 10 shows the predicted glucose profile for the same representative patient. Figure 11 refers to population results, showing the VAF for multi look-ahead $\tau = 10$, 20 [min].

C. Exercise test

For the exercise test it was decided to use only respiration rate and heart rate to forecast glucose evolution. Results are shown in Fig. 7.

IV. Discussion

Online subspace-based predictor models were applied to the problem of short-term prediction of T1DM glycemia. Predictor coefficients were estimated directly from data, with no prior information about the underlying mechanisms generating the time series. No warm-up period was requested by the algorithms, nor initial guesses for the initialization of the coefficients. From an implementation point of view, the

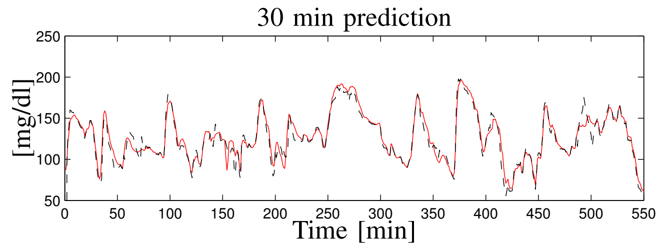

Fig. 10. Representative patient in ambulatory conditions. No-vital signs case. Predicted glucose profiles. CGMS measurements (red) vs. prediction obtained using glucose rate of appearance and insulin in plasma on a 30-minutes prediction horizon (dashed black)

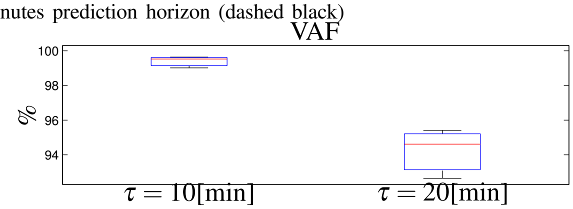

Fig. 11. Population study. No vital-signs case. Variance Accounted For. *Left* 10 min prediction, *Right* 20 min prediction. Each box presents results over the considered population. The central mark is the median, the edges of the box are the 25th and 75th percentiles.

approach is attractive, amounting only to LQ decompositions of appropriately organized input-output Hankel matrices.

Multi-step predictions were evaluated, the main objective of the investigation being the development of data-driven predictors able to overcome the limitations arising from the lack of an accurate and individualized glucose metabolism model in diabetes and that with the least possible user intervention can be included in an advisory tool [1].

Indeed, besides being of interest on its own right, the proposed approach to online prediction can be included in a predictive control framework [25] to the purpose of glycemia regulation. Along this line, introducing the future control inputs u_k, the predictors can be re-written as:

$$\begin{bmatrix} \hat{Y}_{k+1|k} \\ \hat{Y}_{k+2|k} \\ \vdots \\ \hat{Y}_{k+\tau|k} \end{bmatrix} = \begin{bmatrix} \Gamma_1 \\ \Gamma_2 \\ \vdots \\ \Gamma_\tau \end{bmatrix} Z_{[k_0,k)} + \begin{bmatrix} \Lambda_1 & 0 & \cdots & 0 \\ \Lambda_2 & \Lambda_1 & \ddots & \vdots \\ \vdots & \vdots & \ddots & 0 \\ \Lambda_\tau & \Lambda_{\tau-1} & \cdots & \Lambda_1 \end{bmatrix} U_{[k,\tau)} \quad (14)$$

where $Z_{[k_0,k)}$ accounts for the past measured input-output signals up to time instant k, e.g., previously injected insulin, glucose rate of appearance after a meal challenge and glucose from the patient's sensor, $U_{[k,\tau)}$ is the sequence of optimal control "advices" from the optimization of an appropriate cost function [26], e.g. "take 3 units of insulin" or "eat 50 grams of carbohydrate", Γ is given in (9) and

$$\Lambda_i = \hat{C}\hat{\bar{A}}^{i-1}\hat{B} + \sum_{j=1}^{i-1} \hat{C}\hat{\bar{A}}^{i-j-1}\hat{K}\Lambda_j \quad (15)$$

It is this flexibility that, in the author's opinion, makes the merits of this type of predictors.

Long VARX models (5) have been recursively estimated to obtain the predictor coefficients. However, model reduction may also be performed by means of state estimation via

SVD followed by identification of the system matrices, performing the usual steps of subspace identification [27]. Once A, B, C, D, K are determined, (lower order) matrices Γ, Λ can be recomputed and new predictors (10) are calculated, the price to pay being that of minor prediction accuracy. The difficulty here, in the specific diabetes application, stands in the model order selection and validation. Therefore, a procedure that overcomes this limitations (as in the case of the proposed predictors) is worth pursuing.

V. Conclusions and future work

The paper dealt with the recursive estimation of multi-step short-term T1DM blood glucose predictors in various real life situations, exploiting the interplay between previously injected insulin, meal intake and vital signs. Future work will be devoted to the integration of the presented predictors in a totally data-driven subspace predictive control framework to control glycemia in T1DM patients. To that end, an on-line re-calibration module for the CGM sensor as well as an interstitium-to-blood glucose dynamics model will need to be developed. In addition, further work is necessary to investigate optimal experimental conditions and protocols in order to obtain data suitable for identification purposes without contributing to higher patient risk.

VI. Acknowledgments

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