# Glucose Concentration can be Predicted Ahead in Time From Continuous Glucose Monitoring Sensor Time-Series

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***Abstract*—A clinically important task in diabetes management is the prevention of hypo/hyperglycemic events. In this proof-of-concept paper, we assess the feasibility of approaching the problem with continuous glucose monitoring (CGM) devices. In particular, we study the possibility to predict ahead in time glucose levels by exploiting their recent history monitored every 3 min by a minimally invasive CGM system, the Glucoday, in 28 type 1 diabetic volunteers for 48 h. Simple prediction strategies, based on the description of past glucose data by either a first-order polynomial or a first-order autoregressive (AR) model, both with time-varying parameters determined by weighted least squares, are considered. Results demonstrate that, even by using these simple methods, glucose can be predicted ahead in time, e.g., with a prediction horizon of 30 min crossing of the hypoglycemic threshold can be predicted 20–25 min ahead in time, a sufficient margin to mitigate the event by sugar ingestion.**

***Index Terms*—Auto-regressive model, diabetes, hypoglycemia, polynomial model.**

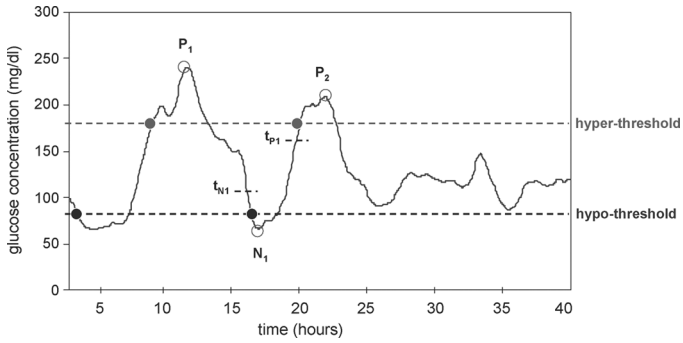


Fig. 1. Subcutaneous sensor glucose concentration time-series in representative subject #1. The dots denote the points at which normal range thresholds are crossed and alerts should be generated. The other symbols P1, P2, N1, tN1, and tP1 will be discussed later (Section IV-B) and denote critical points of the time-series for the quantitative assessment of the prediction algorithms.

## I. Introduction

GLUCOSE is the most important fuel for human beings and its level in the blood is precisely controlled by insulin by a negative feedback system. In diabetic patients, the body does not secrete insulin (type 1 diabetes) or derangements in both insulin secretion and action (type 2 diabetes) occur. Presently, diabetes affects over 150 millions of persons in the world (95% of whom have type 2 diabetes) and 1 over 20 adults. Diabetes therapy is mainly based on insulin and drug administration, diet, and physical exercise, tuned according to self-monitoring of blood glucose levels 3–4 times a day. However, given the inefficiency of this approach, blood glucose concentration in diabetic patients often goes outside the normal range (70–180 mg/dl). Hyperglycemia mostly affects long-term complications, such as neuropathy, retinopathy and cardiovascular and heart diseases, while hypoglycemia (e.g., due to a larger dose of insulin relative to ingested carbohydrates) is of dramatic concern in the short-term, since even mild or moderate hypoglycemia can rapidly turn into dangerous episodes, possibly also leading to hypoglycemic coma. In particular, nocturnal hypoglycemia is especially critical because of the difficulty for patients to recognize its symptoms during sleep.

Recently, several sensors have been developed which allow continuous glucose monitoring (CGM) for several days [5]. CGM systems are noninvasive or minimally-invasive, and, in many cases, the fact that they are portable can allow their use in patient daily life. Although the clinical validation of CGM devices is for some aspects still under way, there is a general agreement that in the near future these devices will enable the tuning of appropriate changes in the daily management of diabetes in order to achieve better metabolic control. In many clinical situations, an improvement of the therapy could be achieved by embedding in a CGM system a tool able to generate alerts when the glucose concentration exceeds the normal range thresholds [1], e.g., in correspondence to the dots of the CGM representative time-series of Fig. 1. However, it would be much more preferable to prevent hypo/hyperglycemic events before they occur, e.g., by generating an alert, say, 20–30 min ahead of time. This gain in time would allow e.g., to prevent hypoglycemia, since it is comparable, if not greater, than the interval required for an ingested sugar to reach the blood. Some methods have been proposed which generate alerts when the current trend of the glucose concentration profile suggests

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that hypoglycemia is likely to occur within a short time. For instance, in [3] an hypoalert is generated when, on the basis of first-order linear extrapolation of glucose obtained from its last two/three samples, there is the risk that glucose concentration will cross the 70-mg/dl threshold within 20 min. A similar methodology is used in [4].

An improvement in the development of algorithms to prevent hypo/hyperglycemic events can be obtained by generating hypo/hyperalerts on the basis of ahead-of-time prediction of glucose concentration by using past CGM data and suitable time-series models. The possibility of predicting glucose concentration from its past history was originally suggested by Bremer and Gough [2], who, by considering published literature glucose concentration profiles (measured in blood for up to 40 hr. every 10 min), qualitatively concluded that a simple linear time-invariant model, preliminarily identified in each time-series against the first half of the data, allows the estimation of "satisfactory" 10-min ahead-of-time glucose level predictions in a variety of glycemic states. The purpose of the present proof-of-concept paper is to build on [2] and to quantitatively assess whether or not glucose levels can be predicted ahead in time by exploiting time-series models fitted against past glucose values provided by a CGM device. In particular, we consider two simple prediction methods, both potentially usable on-line. The first method is based on the description of the past glucose data through a 1st order polynomial model. In the second method, past glucose data are described by a first-order autoregressive (AR) model. In both methods, at each sampling time, a new set of model parameters is first identified by means of weighted least squares techniques. Then, the model is used to forecast glucose level for a given prediction horizon (PH). The data base consists of time-series of glucose concentration monitored every 3 min in 28 diabetic volunteers for nearly 48 h by a minimally invasive commercial CGM device, the Glucoday [7]. Results demonstrate that glucose can be predicted ahead in time, e.g., with a prediction horizon of 30 min crossing of the hypoglycemic threshold can be predicted 20–25 min ahead in time, a sufficient margin to mitigate the event by sugar ingestion.

## II. Prediction Strategies

The problem is to assess whether or not predicting ahead in time glucose concentration by means of CGM data is feasible and we approach it by considering two methods. In the first one, glucose time-series is described, locally, by a first-order polynomial

$$\mathrm{u_i} = \alpha \mathrm{t_i} + \beta \tag{1}$$

while, in the second one, an AR model of first-order (see Conclusions for comment on model order), corresponding to the following time-domain difference equation

$$\mathrm{u_i} = \mathrm{a u_{i-1}} + \mathrm{w_i} \tag{2}$$

is considered. In (2), $\mathrm{i} = 1, 2, \ldots \mathrm{n}$ denotes the order of glucose samples collected till the $n$th sampling time $\mathrm{t_n}$ and $\{\mathrm{w_i}\}$ is a random white noise process with zero mean and variance equal to $\sigma^2$. The prediction strategy is as follows (Fig. 2). Let $\theta$ denote the vector of the parameters of the model employed to describe the glucose time-series, i.e., $\theta = (\alpha, \beta)$ for (1) and $\theta = (\mathrm{a}, \sigma^2)$ for (2). At each sampling time $\mathrm{t_n}$, a new value of $\theta$ is first determined by fitting the model against past glucose data $\mathrm{u_n}, \mathrm{u_{n-1}}, \mathrm{u_{n-2}}, \ldots$ by weighted linear least squares. Once $\theta$ is determined, the model is used to calculate the prediction of glucose level T steps ahead, i.e., $\hat{\theta}_{\mathrm{n+T}}$. For a sampling interval of 3 min, a value of T equal to 10 or 15 corresponds to a PH equal to 30 or 45, respectively. The value $\hat{\theta}_{\mathrm{n+T}}$ is calculated in a straightforward fashion from (1) for the polynomial model, while, when an AR model is considered, the time-domain difference equation of (2) is used iteratively for $\mathrm{i} = \mathrm{n}+1, \mathrm{n}+2, \ldots, \mathrm{n}+\mathrm{T}$ with $\mathrm{w_i} \equiv 0$.

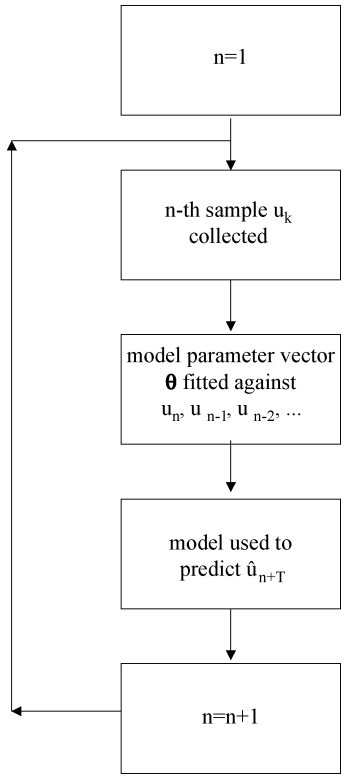


Fig. 2. A schematic representation of the prediction approach.

Both methods are based on time-varying models. The necessity of having a time-varying $\theta$ is obvious in the model of (1). For the AR model of (2), the use of a time-invariant $\theta$, e.g., identified in a burn-in interval, would produce inaccurate predictions (see also Remark 1 in Section IV-B) because of the nonstationarity of CGM time-series, which calls for a time-varying modeling strategy [2].

All the past data $\mathrm{u_n}, \mathrm{u_{n-1}}, \ldots, \mathrm{u_1}$, participate, with different relative weights, to the determination of $\theta$. The way with which past data are weighted is a key aspect in model fitting. Here, we have assigned the weight $\mu^{\mathrm{k}}$ to the sample taken k instants before the actual sampling time, i.e., $\mu^{\mathrm{k}}$ is the weight of the sample at time $\mathrm{t_{n-k}}$ $(\mathrm{k} = 0, 1, \ldots, \mathrm{n}-1)$ [6]. The parameter $\mu$ behaves like a *forgetting factor*, a parameter typically introduced in the modeling of nonstationary processes in order to improve

the fit of the most recent data [6], [8]. If the forgetting factor were not used (which is equivalent to letting $\mu = 1$), glucose samples collected tens of hours, if not days, before the actual sampling time would influence prediction, with a significant deterioration of the algorithm capability to promptly track changes in the signal, in particular those due to perturbations, e.g., meals (see also Remark 2 in Section IV-B). The forgetting factor, thus, belongs to the range (0,1) and its value regulates the length of the "memory" of the past data which participate to the determination of $\theta$. For instance, with $\mu = 0.2$ the memory is relatively "short." In fact, weights are equal to 1, 0.2, 0.04, 0.008, ..., so, for a sampling interval of 3 min, the glucose level collected 9 min earlier than the current sampling time has, in the determination of $\theta$, a relative weigth 125 times (1/0.008) smaller than that of the last sample. Conversely, with $\mu = 0.8$ the memory is relatively "long" (weights are 1, 0.8, 0.64, 0.512, ...), so the relative weigth of the above samples is reduced to $\sim$2 (1/0.512). A closed-form expression has been used to determine $\theta = (\alpha, \beta)$ of (1), while a recursive least squares algorithm implemented in the Matlab System Identification Toolbox (Mathworks Inc, Natick, MA) was employed to determine $\theta = (\mathrm{a}, \sigma^2)$ of (2) [6].

The described prediction approach is simple but rather general, e.g., it is independent of the sampling rate of the CGM sensor, and is, thus, well suited to the twofold proof-of-concept: demonstrate that glucose levels can be predicted ahead of time by exploiting past CGM data and show clinical usefulness of glucose prediction by assessing the temporal margin with which hypo/hyperglycemic events can be predicted ahead of time.

## III. Data Base

The prediction algorithms were tested on Glucoday time-series, obtained from 28 Type 1 diabetic patients. GlucoDay is composed of a subcutaneous microdialysis probe which can be connected to a light portable apparatus worn with a belt for the 24–48 h home monitoring and provides glucose levels every 3 min. We refer the reader to [7] for details. A representative Glucoday time-series is displayed in Fig. 1.

Since Glucoday does not have on-board any pre-processing unit, before applying the prediction algorithms, it was necessary to remove large spikes which occasionally corrupt the time-series when temporary probe misplacements are caused by episodic patient movements. To do this, data were undertaken to flat low-pass filtering (first-order Butterworth filter with cutoff frequency, normalized to half the sampling rate, $\omega_{\mathrm{n}} = 0.05$).

## IV. Results

### A. Prediction Profiles

Table I offers a first quantitative assessment of the results in all 28 subjects by reporting median and 10%–90% percentiles of the mean square prediction error (MSPE) and of the energy of the second-order differences of the predicted profile (ESOD). MSPE measures the closeness of the predicted profile to the original one, while ESOD reflects the presence of (spurious) oscillations in the predicted profiles and, thus, their potential facility of use in the subsequent stage of alert generation. Fig. 3 (left) shows, for PH of 30 min, the original (solid) versus the predicted (thin line) time-series of the polynomial model in the representative subject #1 of Fig. 1 for $\mu = 0.2$ (top), $\mu = 0.5$ (middle), and $\mu = 0.8$ (bottom). Fig. 3 (right) shows the results of the AR model. Fig. 4 shows the results in another representative subject (#2) but with PH of 45 min. From a qualitative point of view, Figs. 3 and 4 qualitatively suggest that the performance of both methods is acceptable, with the AR model, especially for $\mu = 0.8$, being significantly more prompt than the polynomial model in tracking ascending trends of the measured time-series (see Section IV-B for a quantitative analysis). MSPE is however similar with both the models, denoting that none of the two is clearly superior to the other. Also, Figs. 3 and 4 show that, with the same $\mu$, the predicted profiles of the polynomial model are slightly smoother than those of AR model (as also confirmed by ESOD values in Table I), but exhibit a more consistent overshooting in correspondence to changes in the sign of the first time-derivative. As far as influence of PH on quality of prediction is concerned, an increase of PH causes, as expected, a larger prediction error and wider oscillations in predicted profiles. This is well visible from Figs. 3 and 4 and is reflected in MSPE and ESOD values with $\mathrm{PH} = 45$ much higher than with $\mathrm{PH} = 30$. Finally, Figs. 3 and 4 and Table I well illustrate the role of the forgetting factor $\mu$. A low value of $\mu$ ("short" memory of past glucose, top panels) renders the prediction algorithm able to track changes in the time-series trend (MSPE relatively small), at the price of a higher sensitivity to noise (ESOD relatively large). In contrast, a high value of $\mu$ ("long" memory of past glucose, bottom panels) results in a more stable prediction profile (ESOD relatively small), at the cost of losing the ability to promptly track changes in the glucose trend (MSPE relatively

TABLE I
Mean Square Prediction Error (MSPE) and Energy of Second Order Differences (ESOD): Median Values and (10%–90%) Percentiles

| | | POLYNOMIAL | | AUTO-REGRESSIVE | |
|---|---|---|---|---|---|
| **μ** | **PH** | **MSPE** | **ESOD** | **MSPE** | **ESOD** |
| 0.2 | 30 | 318 (129, 632) | 42038 (9653, 134480) | 336 (139, 827) | 85684 (14551, 785582) |
| | 45 | 1035 (414,1809) | 89247 (20403, 304156) | 1218 (454, 3428) | 228895 (34250, 2572683) |
| 0.5 | 30 | 374 (161, 677) | 8645 (2656, 31699) | 353 (146,924) | 35925 (6657, 302364) |
| | 45 | 1048 (415, 2250) | 17105 (5191, 61849) | 1200 (480, 3690) | 90780 (14543, 917982) |
| 0.8 | 30 | 598 (260, 892) | 675 (276, 2179) | 413 (175, 753) | 8420 (1988, 51602) |
| | 45 | 1357 (640, 3119) | 1083 (438, 3523) | 1258 (537, 2195) | 18303 (3995, 120293) |

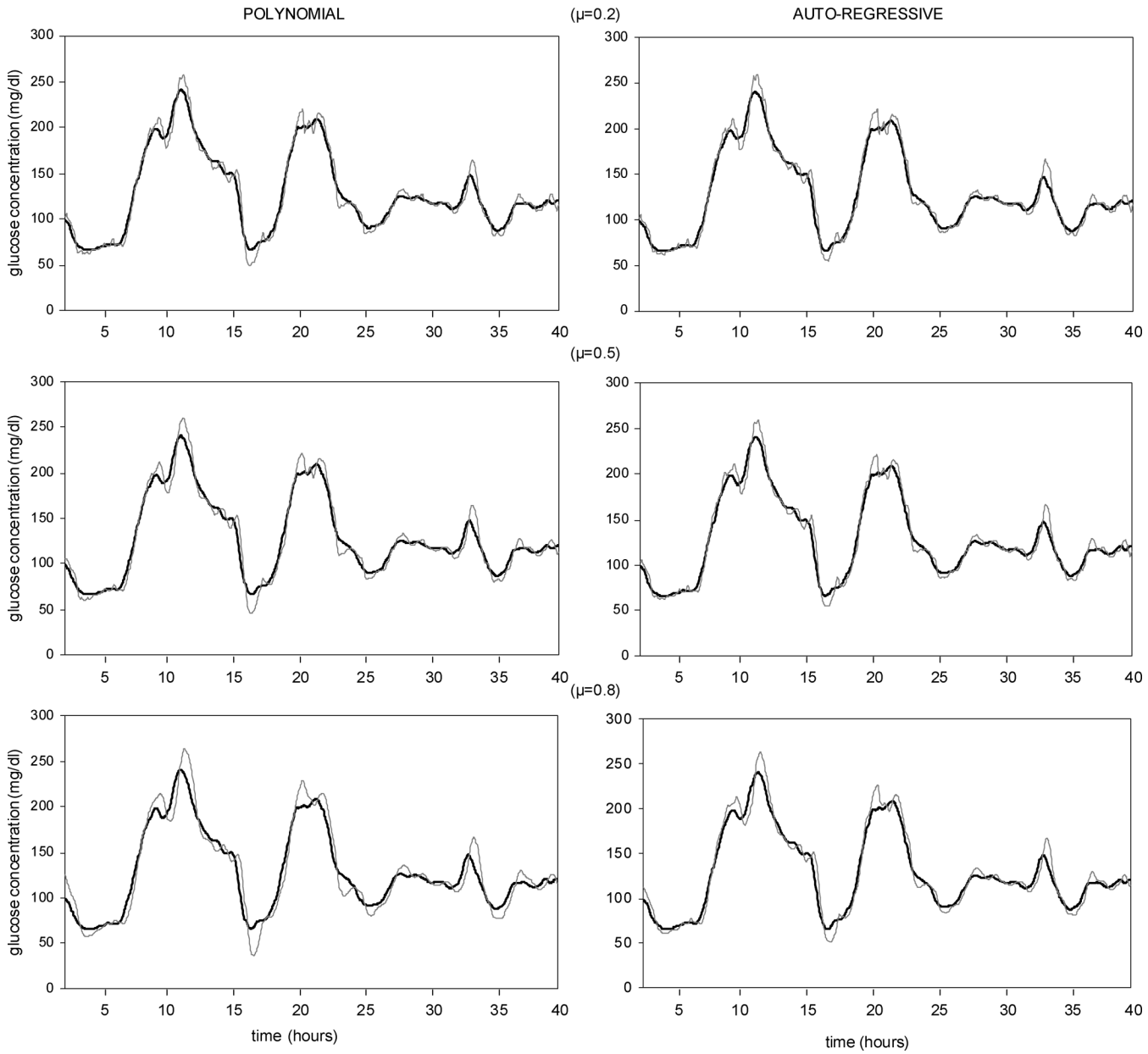


Fig. 3. Representative subject #1. Left. Polynomial model. Original (solid) versus predicted (thin line) time-series ($\mathrm{PH} = 30$) with $\mu = 0.2$ (top), $\mu = 0.5$ (middle), and $\mu = 0.8$ (bottom panel). Right. Same as in the left panels, with AR model.

large). In a patient perspective, oscillations in the prediction profile are obviously undesirable, since they can facilitate the generation of false hypo/hyperalerts. On the opposite, a delay of the prediction profile comparable to PH (or larger) would make the approach useless in practice. It is, thus, crucial to quantitatively evaluate the delay in the predicted profile. This quantification in each individual CGM time-series will also allow us to assess the average performance of the two prediction strategies in the entire data base.

### *B. Assessment of Delays*

An intuitive approach would be to assess the delay with which significant points of the original can be detected from the predicted glucose time-series. For instance, one could identify major peaks and nadirs in the original time-series (see e.g., Fig. 1, where only two peaks, $\mathrm{P}_1$ and $\mathrm{P}_2$, and one nadir, $\mathrm{N}_1$, are pointed out) and in the predicted one and then measure their relative delay. However, these results (not shown) would offer a too pessimistic portrait of the prediction performance, since peaks and nadirs are the points where the prediction delay is the largest. Therefore, it is more appropriate to quantify the delay between the predicted and original glucose curve during negative and positive trends. In particular, we have measured the times at which some thresholds are crossed in the original and in the predicted glucose time-series. A natural choice for these thresholds would be the levels that define the normal glycemic range (70–180 mg/dl). However, since in our 28 time-series these levels were seldom exceeded, we have defined a wider set of "evaluation" threshold levels as follows. Having identified in each time-series peaks and nadirs, we have considered the

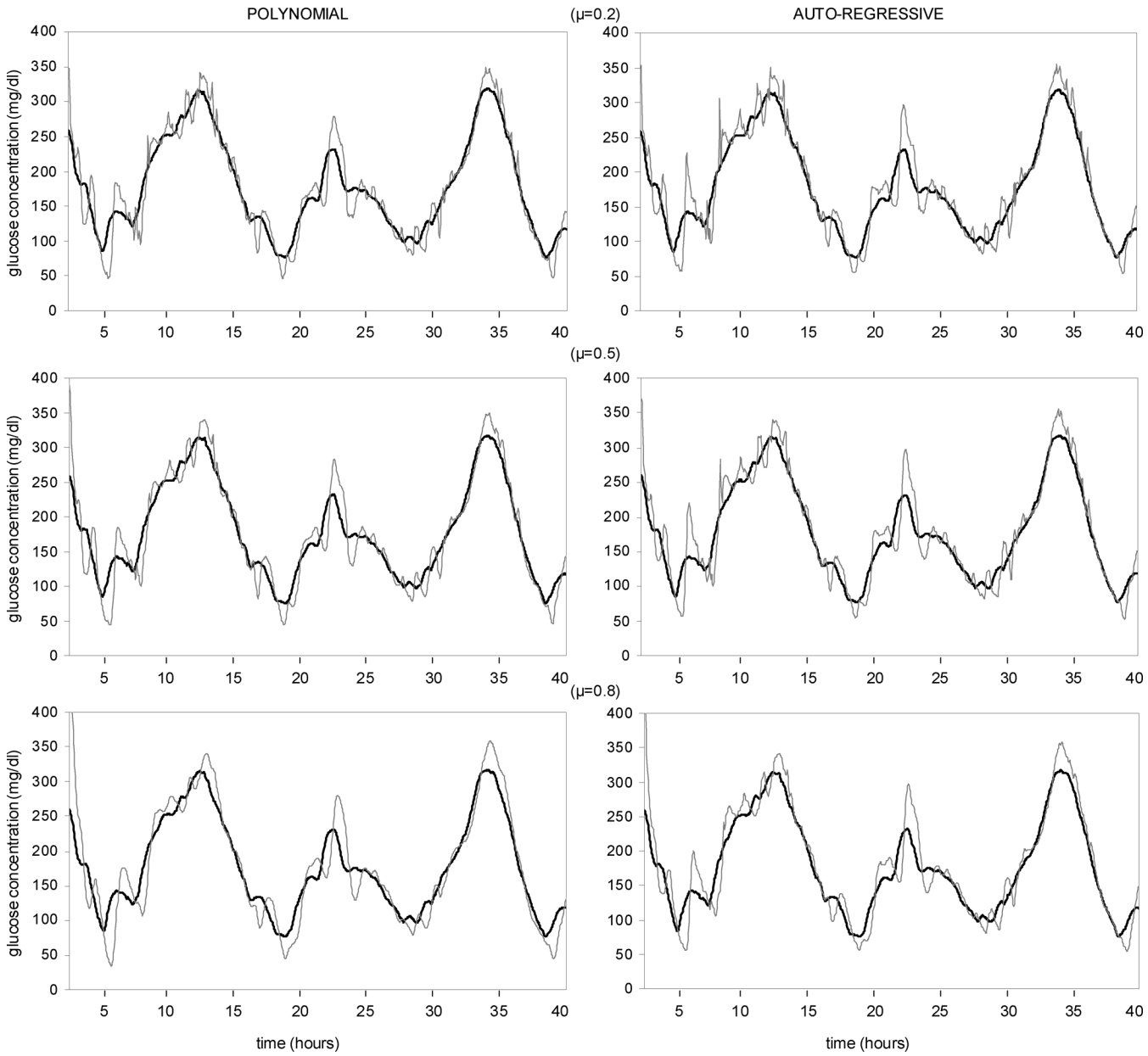


Fig. 4. Representative subject #2. Left. Polynomial model. Original (solid) versus predicted (thin line) time-series $(\mathrm{PH} = 45)$ with $\mu = 0.2$ (top), $\mu = 0.5$ (middle), and $\mu = 0.8$ (bottom panel). Right. Same as in the left panels, with AR model.

peak-to-nadir and nadir-to-peak distances. When the trend of the original time-series is negative, the threshold is placed at the 75% of the peak-to-nadir distance; similarly, when the trend is positive, the threshold is placed at the 75% of the nadir-to-peak distance. To exemplify the strategy, in Fig. 1 we evidence by small horizontal dashed lines the thresholds of the first negative trend $(\mathrm{tN}_1)$ and of the first positive trend $(\mathrm{tP}_1)$. Looking at all 28 time-series, there are 102 thresholds during positive and 106 during negative trends.

The average delays for which threshold crossings can be detected are reported [together with standard deviation (SD)] in Table II for $\mu = 0.2, 0.5, 0.8$. As expected, the smaller is $\mu$, the smaller the delay, but the greater its variability relative to the mean, with the inherent increase of the possibility of generating false alarms. However, the main result emerging from Table II is that crossing of some preselected threshold levels can be detected from the predicted time-series with a delay which is significantly lower than PH. For instance, with the polynomial model and $\mathrm{PH} = 45$ min, even with $\mu = 0.8$ (which gives the smoothest profile but the largest delay), there is, on average, a delay of only 19.56 min in crossing the positive trend thresholds and a delay of 12.96 min in crossing the negative trend thresholds. With AR model, these delays are reduced to 10.06 and 12.42 min, respectively. In other words, even in the worst case, there is a gain in time of nearly 30 min usable for alert generation. Overall, irrespectively of the value of $\mu$, the relative performance of polynomial and AR models is quite similar during negative trends; in contrast, AR performs better during positive trends, as already seen in commenting Figs. 3 and 4. This is also visible in the two representative subjects, and may

TABLE II
AVERAGE DELAY WITH SD WITH WHICH THRESHOLDS CROSSINGS ARE DETECTED IN THE 28 SUBJECTS. TIMES ARE EXPRESSED IN MINUTES

| | | POLYNOMIAL | | AUTO-REGRESSIVE | |
|---|---|---|---|---|---|
| $\mu$ | PH | positive trends delay (SD) | negative trends delay (SD) | positive trends delay (SD) | negative trends delay (SD) |
| 0.2 | 30 | 4.65 (12.48) | -0.48 (12.17) | 1.41 (15.48) | 1.19 (13.03) |
| | 45 | 9.74 (17.84) | 3.11 (15.67) | 6.74 (19.29) | 6.08 (14.99) |
| 0.5 | 30 | 6.53 (12.55) | 0.93 (13.48) | 2.15 (15.63) | 2.35 (13.03) |
| | 45 | 12.41 (17.97) | 5.46 (16.06) | 8.09 (19.37) | 7.42 (15.27) |
| 0.8 | 30 | 11.94 (16.65) | 6.54 (13.95) | 3.79 (18.01) | 5.29 (12.63) |
| | 45 | 19.56 (19.89) | 12.96 (18.50) | 10.06 (21.44) | 12.42 (14.97) |

reflect the fact that the energy of the first time-difference during positive trends is, on average, higher than that during negative trends (computation not reported). In conclusion, AR is preferable to polynomial modeling because it is more accurate even when relatively large values of $\mu$ are considered, a feature which will be important in the next steps of research, when the problem of generating hypo/hyperalerts will be explicitly considered.

*Remark 1:* The importance of using a time-varying approach is witnessed from the fact that a time-invariant AR model of first order, with parameters identified in a burn-in interval, would result in predicted profiles with average delays close to the used PH, e.g., 28.12 and 31.67 min, respectively during positive and negative trends, with $\mathrm{PH} = 30$.

*Remark 2:* With the used AR model, the use of the forgetting factor is mandatory. If all the past data were considered with equal weight, i.e., $\mu = 1$, smooth but consistently delayed predicted profiles with no practical usefulness would be obtained, e.g., with $\mathrm{PH} = 30$ the average delay would be of 26.58 and 31.47 min during positive and negative trends, respectively.

*Remark 3:* The results presented in this paper have been obtained on 3 min sampled Glucoday glucose time-series, which were digitally prefiltered in order to remove artifacts. For these time-series with the considered PH, the AR model of order 1 was the most reliable to obtain a clinically significant prediction performance (AR models of higher orders often provided unstable predictions). The extent to which these specific results also hold in a more general context, i.e., different prefiltered Glucoday or other CGM sensor time-series, remains to be further investigated. In fact, the chosen order of the AR model and the value of the forgetting factor should reflect the sampling rate (e.g., the higher is the sampling frequency, the higher should be the model order) as well as the signal-to-noise ratio (SNR) of the sensor data (e.g., the lower the SNR, the higher the forgetting factor, at the cost of larger delays). Also the maximum allowable PH should be matter of investigation. With the present data, $\mathrm{PH} = 45$ seemed to lead to acceptable predicted profiles, while larger values resulted in wide oscillations which may hinder their exploitation for the generation of hypo/hyperglycaemic alerts. In general, the maximum allowable PH should have probably to reflect both SNR and sampling rate (e.g., the higher the SNR and/or the sampling rate, the higher the maximum allowable PH).

## V. CONCLUSION

In this work two simple prediction methods have been applied for the first time to real CGM time-series. CGM time-series are described by a model with fixed structure but with time-varying parameters which, at each sampling time, are re-adjusted on the basis of the newly collected glucose sample. Since the model has to describe the time-series only "locally," its complexity is kept modest, a crucial aspect for using prediction algorithms in real-time. The performance of the algorithms was assessed by considering both classical signal estimation indices (Table I) as well as novel delay indices which are important in a clinical/patient context (Table II). Results obtained in 28 CGM Glucoday time-series quantitatively demonstrate not only that glucose prediction from past data is feasible (Figs. 3 and 4), but also that the performance of prediction algorithms is adequate for preventing hypo/hyperglycemic events (Table II). In particular, with $\mathrm{PH} = 30$ one can speculate that crossing of hypo/hyperglycemic thresholds of 70 and 180 mg/dl can be predicted more than 20–25 min ahead in time, a margin which can have a clinical relevance, for instance for preventing nocturnal hypoglycemic shocks.

The promising results reported in this paper should encourage further development of this research line. For instance, it could be worthwhile investigating, also with data provided by other CGM sensors, more sophisticated autoregressive models, e.g., ARI, ARIMA, as well as Bayesian filtering approaches. Finally, a critical problem to be faced in the future concerns the generation of alerts on a solid statistical basis in order to properly deal with the potentially serious problem of false/missing events.

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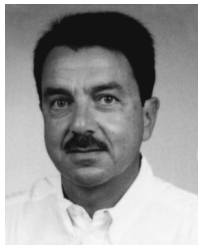

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