

A New Index to Optimally Design and Compare Continuous Glucose Monitoring Glucose Prediction Algorithms

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Abstract

Background: Continuous glucose monitoring (CGM) data can be exploited to prevent hypo-/hyperglycemic events in real time by forecasting future glucose levels. In the last few years, several glucose prediction algorithms have been proposed, but how to compare them (e.g., methods based on polynomial rather than autoregressive time-series models) and even how to determine the optimal parameter set for a given method (e.g., prediction horizon and forgetting) are open problems.

Methods: A new index, J , is proposed to optimally design a prediction algorithm by taking into account two key components: the regularity of the predicted profile and the time gained thanks to prediction. Effectiveness of J is compared with previously proposed criteria such as the root mean square error (RMSE) and continuous glucose-error grid analysis (CG-EGA) on 20 Menarini (Florence, Italy) Glucoday[®] CGM data sets.

Results: For a given prediction algorithm, the new index J is able to suggest a more consistent and better parameter set (e.g., prediction horizon and forgetting factor of choice) than RMSE and CG-EGA. In addition, the minimization of J can reliably be used as a selection criterion in comparing different prediction methods.

Conclusions: The new index can be used to compare different prediction strategies and to optimally design their parameters.

Introduction

IN DIABETES RESEARCH, particular attention has been paid in the last few years to noninvasive or minimally invasive portable continuous glucose monitoring (CGM) devices.^{1,2} One of the major advantages introduced by these systems is that they can be exploited to mitigate hypo-/hyperglycemic events in real time.³ In fact, most of the commercial CGM sensors embed an alarm generation that alerts the patient when glucose concentration exceeds hypo- or hyperglycemia thresholds.^{4,5} However, it would be much more preferable to prevent this kind of threatening episodes before they occur,⁶ e.g., by generating an alert 20–30 min ahead of time on the basis of ahead-of-time prediction of glucose concentration computed from past CGM data and suitable time-series models.

Recently, several methods, e.g., based on polynomial⁷ or autoregressive^{8–10} time-series models, Kalman filtering,¹¹ and artificial neural networks,¹² have been developed and proposed to predict (e.g., 30–45 min ahead of time) glucose concentration from past CGM data (possibly weighted via a forgetting factor [μ]). In all these methods, once a model structure (e.g., autoregressive time-series model) is fixed, some model parameters (e.g., prediction horizon [PH] and μ) need to be set. In spite of the significant number of articles

published on prediction from CGM data in the last years, how to determine the optimal set of a prediction algorithm parameters and how to choose the best prediction algorithm among several candidates (e.g., models with different structure and order) are still open problems. Identifying correct parameter values in a specific prediction algorithm is important, as it can be easily illustrated by resorting to the example displayed in Figure 1. In particular, Figure 1 shows two predictions, labeled as A and B, obtained, for PH = 30 min, from a representative Menarini (Florence, Italy) Glucoday[®] CGM time-series (gray dashed line) taken from a larger dataset.¹³ The prediction algorithm used⁸ is based on a first-order polynomial model [POL(1)] and is characterized by a user parameter μ , termed the forgetting factor (the higher μ , the longer the memory of the past data used to determine the time-series model parameters), which must be suitably chosen within the range (0,1). Prediction A (black thick line), obtained with $\mu = 0.95$, is very regular, but the amount of time gained because of the prediction is close to zero, meaning that, in practice, the predicted profile, despite its nice smoothness, has no clinical utility. For instance, the hyperglycemic threshold crossing at time 26.4 h is, in predicted profile, at time 27.3 h, so that the alert could be generated only at time 26.8 h. On the other hand, whereas prediction B (black thin line), obtained

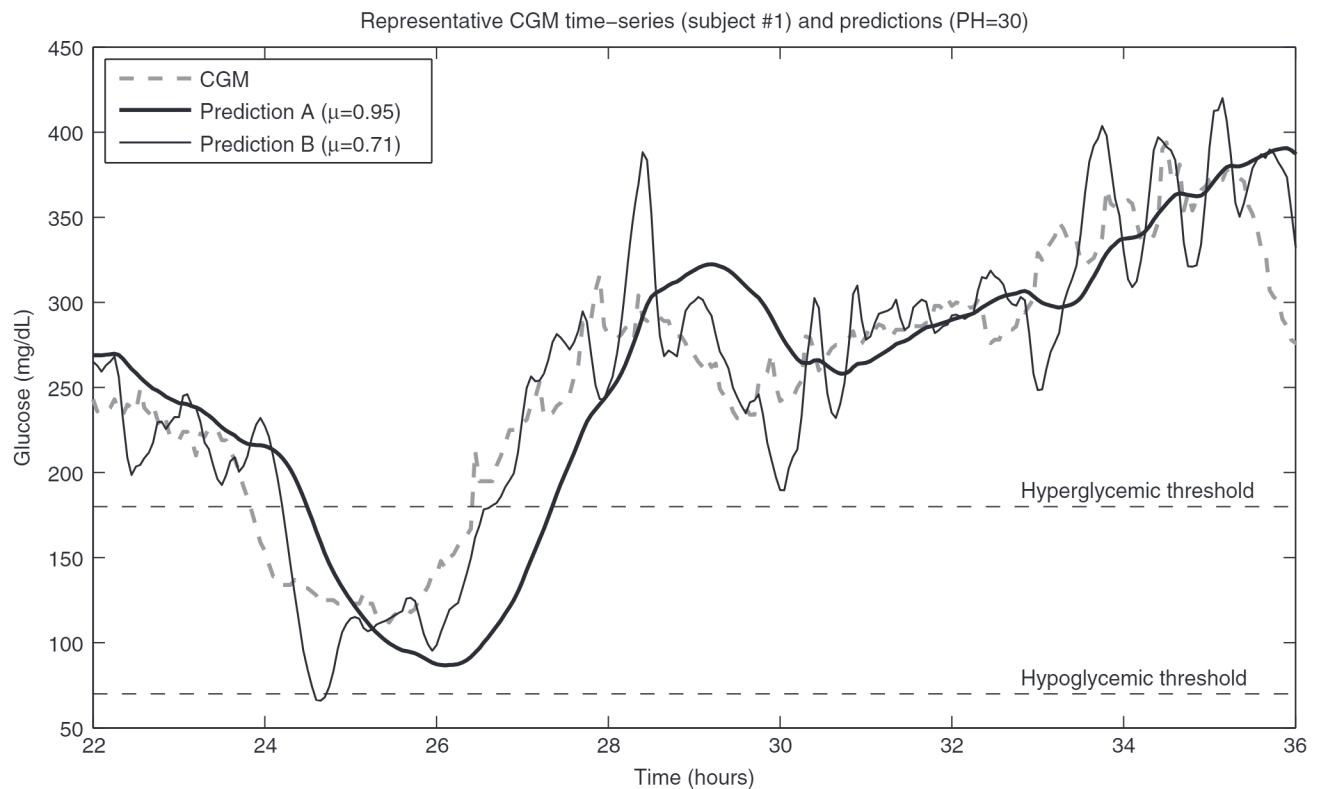


FIG. 1. Representative Menarini Glucoday continuous glucose monitoring (CGM) time-series (gray dashed line) and profile predicted by first-order polynomial model with set A (black thick line, forgetting factor $[\mu]=0.95$) and B (black thin line, $\mu=0.71$), with prediction horizon (PH)=30 min in both cases (data taken from Maran et al.¹³).

with $\mu=0.71$, provides a time gain close to PH, the profile is very unstable, presenting wide oscillations that will eventually cause in practice an elevated number of false alerts (e.g., look at the false hypo-alert around 24.5 h). It is evident that the choice of μ is crucial to determine the performance of the prediction algorithm. Ideally, one would like to have at the same time a large time interval gained due to prediction (to facilitate hypo-/hyperglycemic event prevention) and a stable predicted profile (to limit the risk of false alerts). Unfortunately, the time gained and regularity are inversely related, i.e., the higher the time gained, the higher the irregularity. This calls for an appropriate index able to balance these contrasting requirements.

In the literature, how to determine the unknown parameters of a prediction algorithm in order to optimize its performance has been only partially debated. Sparacino et al.⁸ qualitatively suggested to somewhat combine the information contained in the energy of the second-order differences (ESOD) of the predicted time-series and the delay measured in crossing some fixed thresholds between the original and the predicted CGM profiles. Gani et al.⁹ resorted to the root mean square error (RMSE) between original and predicted CGM data and on an average delay introduced by the prediction. Palerm et al.¹¹ proposed to evaluate missed and false detected alarms. The use of continuous glucose-error grid analysis (CG-EGA) was also proposed by Zanderigo et al.¹⁴ pairing the original and the predicted CGM time-series. Eren-Oruklu et al.¹⁰ used the sum of squares of the glucose prediction error, the relative absolute differences between original and predicted CGM time-series, and CG-EGA.

Unfortunately, all the above indexes and methodologies are not reliable for solving the problems of finding the optimal parameter set and comparing different prediction strategies. Figure 1 supports this statement. In fact, as later explained in the section Use of J, prediction A of Figure 1 corresponds to the best parameter set in terms of CG-EGA, whereas prediction B of Figure 1 corresponds to the best set in terms of RMSE. Clearly, both these parameter sets lead to useless predictions.

In this work we propose a new index that can be used both to find the optimal set of a given prediction strategy and to quantitatively compare the performance of different prediction algorithms according to their prediction usefulness. The index simultaneously considers two merit criteria, i.e., regularity of the predicted time-series and time gained thanks to prediction. The index has a mathematical structure that renders it usable with a generic prediction method. The usefulness and superiority over RMSE and CG-EGA are demonstrated by considering a specific prediction algorithm (based on a polynomial model) and finding the optimal set for its parameters (μ and PH) in 20 CGM Menarini Glucoday datasets.¹³ We also show how the index can be used to compare the overall performance of two different prediction strategies: first-order polynomial versus autoregressive model.

Rationale and Definition of J

In the evaluation of the performance of a prediction algorithm, two important aspects have to be simultaneously considered. In fact, an unstable prediction, such as that labeled B in Figure 1, is of limited utility in practice because it

may cause an elevated number of false alerts. On the other hand, a regular but consistently delayed predicted profile, such as the prediction labeled A in Figure 1, is also of no use because the amount of time gained because of the prediction is close to zero. Thus, regularity and temporal gain (TG) are two key components in evaluating the performance of a prediction algorithm.

As well established in the context of Phillips–Tikhonov regularization,¹⁵ the regularity of a time-series $\mathbf{x} = \{x(1), x(2), \dots, x(N)\}$ of length N can be measured using the ESOD, defined as:

$$\text{ESOD}(\mathbf{x}) = \sum_{i=1}^N \left(\Delta^2(x(i)) \right)^2 \quad (1)$$

(having assumed that samples are equally spaced). In fact, significant oscillations in x are reflected in large values of $\text{ESOD}(\mathbf{x})$.⁸

The TG due to prediction can consider different choices. Here, a measure of an “average” TG is obtained as:

$$\text{TG}(\mathbf{x}, \hat{\mathbf{x}}) = \text{PH} - \text{delay}(\mathbf{x}, \hat{\mathbf{x}}) \quad (2)$$

where PH is the PH used to perform the prediction $\hat{\mathbf{x}}$ and the delay $(\mathbf{x}, \hat{\mathbf{x}})$ between the original and the predicted profiles quantified by the temporal shift k that minimizes the distance between $\mathbf{x}$ and $\hat{\mathbf{x}}$:

$$\text{delay}(\mathbf{x}, \hat{\mathbf{x}}) = \arg \min_k \sum_{i=1}^N (x(i) - \hat{x}(i-k))^2 \quad (3)$$

This definition of delay $(\mathbf{x}, \hat{\mathbf{x}})$ is consistent with that of Gani et al.,⁹ and it is a more general definition than the one used in other works.^{8,12}

In order to build an index that weights Eqs. 1 and 2, we first note that a good prediction should have a low ESOD (to be reliable) and a high TG (to be clinically useful). After a preliminary analysis in which different candidate indexes were tested and compared (not documented here for sake of brevity), the following index was identified as the most suited:

$$J = \frac{\text{ESOD}(\hat{\mathbf{x}})/\text{ESOD}(\mathbf{x})}{\text{TG}(\mathbf{x}, \hat{\mathbf{x}})/\text{PH}} \quad (4)$$

Note that, in Eq. 4, the irregularity of the predicted profile is normalized to the irregularity of original CGM data, and the $\text{TG}(\mathbf{x}, \hat{\mathbf{x}})$ is normalized to the PH used in performing prediction. This normalization is a key ingredient of the index, which is adimensional.

It is worthwhile noting that J has a physiological domain of validity, i.e., the index has no value, e.g., when $\text{ESOD} = 0$.

Assessing J

Database

The database consists of 20 CGM time-series, taken from a larger study,¹³ in type 1 diabetes patients using the Glucoday system. Each time series lasts about 2 days. The sampling period is 3 min. In order to reduce the influence of measurement noise, causal prefiltering is performed by the self-tunable denoising approach of Facchinetti et al.¹⁶

Prediction methods

To assess the usefulness of J , we considered two simple but effective prediction strategies proposed in Sparacino et al.⁸ The first strategy is based on POL(1), whereas the second algorithm is based on a first-order autoregressive model, AR(1). Both methods are time-varying because their parameters are re-estimated every time a new measurement is available, and both are characterized by two parameters: the forgetting factor μ and the prediction horizon PH. For more details on the algorithms, we refer the reader to Sparacino et al.⁸

Remark 1. Even if J index has general usability, in order to test it the specific AR(1) and POL(1) prediction algorithms have been selected, among the several methods for glucose prediction presented in the literature, because their simplicity (in both algorithms the parameter set consists of only two parameters) make them very suitable to the conceptual purpose of the present work.

Use of J

J is tested in three different contexts. First, we consider the prediction strategy POL(1), and we show that J can be used to select the optimal forgetting factor μ . Then, for the same prediction strategy, we show that J can be used to determine the optimal PH. Finally, we illustrate how J can be also used to compare the performance of POL(1) and AR(1). These three applications show possible uses of J in finding the optimal parameter set and/or in comparing the performance of generic prediction methods.

Choice of the optimal μ

We consider the problem of finding the value of the parameter μ that maximizes the performance of POL(1). For the sake of simplicity, we fix PH equal to 30 min. For each of the 20 subjects of the database, we run POL(1) for different μ values (from 0.2 to 1) and compute J and, for comparison, the RMSE and the percentage of erroneous readings in the CG-EGA. For these three indexes, we consider mean and sample SD from the 20 data sets. Figure 2 depicts the mean (black line) and SD (gray area) of the three considered indexes as function of μ . The average RMSE (left panel) presents a minimum value for the optimal $\mu_{\text{opt}} = 0.71$ (circle). However, RMSE behavior is quite flat when μ is in the range 0.4–0.8, suggesting that the RMSE is very sensitive to causal effects. In fact, the difference in terms of RMSE between, e.g., $\mu = 0.4$ and 0.71 is not significant ($P = 0.14$, Wilcoxon rank sum test), even if the difference in the prediction behavior for those two values of μ is large (not shown). Of note is that the SD band is very large for likely all μ values, and in particular the variability is not reduced in correspondence with the μ_{opt} value as one would expect, meaning that RMSE is not appropriate for such a scope. By looking at the middle panel, the average percentage of erroneous readings in the CG-EGA decreases with the increasing of μ and presents a minimum for $\mu_{\text{opt}} = 0.95$ (black circle). However, the CG-EGA is also unable to precisely identify an optimal value for μ . In fact, the difference in terms of erroneous readings between, e.g., $\mu = 0.7$ or 0.95 is not significant ($P = 0.07$), even if, also in this case, the two profiles obtained with the two values would be substantially

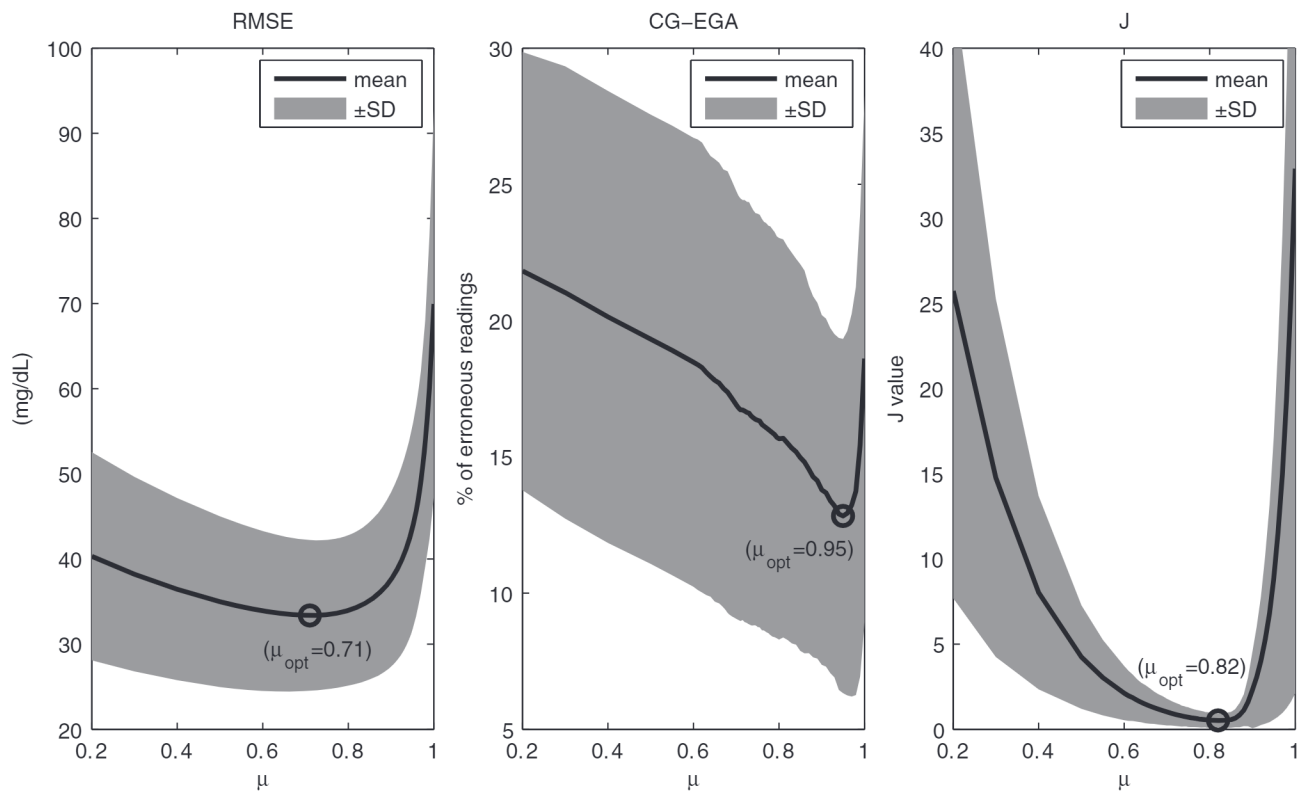


FIG. 2. Root mean square error (RMSE) (**left**), percentage of erroneous readings in continuous glucose-error grid analysis (CG-EGA) (**middle**), and new index J (**right**) as functions of forgetting factor (μ) when the first-order polynomial POL(1) model is used with prediction horizon = 30 min. The black line is the mean value in the 20 subjects, the gray area denotes the inter-individual variability (± 1 SD), and the circle is the minimum value. μ_{opt} , optimal μ .

different (data not shown). One can note that, also for the CG-EGA, the variability between subjects is very large for all μ values, with no reduction in correspondence of the minimum μ_{opt} . Finally, the right panel shows the behavior of the new index J. A well-pronounced minimum is visible for $\mu = 0.82$ (black circle). We can note that, unlike the behavior of the other two indexes, the new index is able to precisely detect the best μ . In fact, according to J, the performance of the prediction becomes significantly worse ($P < 0.01$) than the optimal case when using $\mu < 0.72$ or $\mu > 0.87$, i.e., values very close to the minimum. In addition, the variability of the SD band significantly decreases around the minimum μ_{opt} . This means that, around the optimal value μ_{opt} , the predictions in all the 20 subjects present a similar behavior.

Once the μ_{opt} has been identified for the three merit criteria considered, we can evaluate the correspondent predicted profiles. Figure 3 depicts a detail on two representative time-series (gray dashed lines) taken from the dataset of 20. Predicted profiles obtained with $\mu_{\text{opt}} = 0.71$ (suggested by the RMSE, black thin lines), with $\mu_{\text{opt}} = 0.95$ (suggested by the CG-EGA, gray thin lines), and with $\mu_{\text{opt}} = 0.82$ (suggested by J, black thick lines) are shown. By looking at subject #1 (top panel), it is quite evident that, even if the predicted profile based of the RMSE indication has a satisfactory TG (TG = 13 min, i.e., a hypoglycemic threshold crossing could be predicted with some minutes of advance), the curve is very irregular (ESOD = 85.7) and presents a lot of spurious oscillations, e.g., in the time interval 25–26 h, which would make the curve of difficult utilization in practice, e.g., it would

produce an elevated number of false alerts. This situation can be even better appreciated by looking at subject #2 (bottom panel), which presents a good TG (equals to 15 min) but an elevated instability (ESOD = 47.1), with a significant risk of generating a false hypoglycemic alert at time 6.5 h. Similar results are obtained for the other subjects. This allows the conclusion that the RMSE leads to a suboptimal estimation of μ and, in general, to a suboptimal parameter set.

On the other hand, predicted profiles obtained using the μ_{opt} suggested by the CG-EGA are too smooth in both subjects (ESOD = 11.7 and 5.8, top and bottom panels, respectively) and, in practice, of no clinical utility because the delay is equal to the PH (TG = 0, i.e., threatening events cannot be prevented in any way though the exploitation of prediction algorithms) in both cases. Similar results are obtained for all the other subjects. This allows the conclusion that the CG-EGA also leads to a suboptimal estimation of μ and, in general, to a suboptimal parameter set.

The predicted profiles obtained by using the value $\mu_{\text{opt}} = 0.82$ suggested by J seem a good compromise between two opposite needs because they are sufficiently regular (ESOD = 25.8 and 13.9, top and bottom panels, respectively) and present satisfactory TG values (TG = 10 and 9 min, respectively). In particular, focusing on the bottom panel, it is apparent that the prediction suggested by J does not generate any false alerts as those suggested by the previous indexes would do. Similar results have been obtained for the other subjects. This allows the conclusion that J is able to properly weight both irregularity and delay of prediction, allowing the

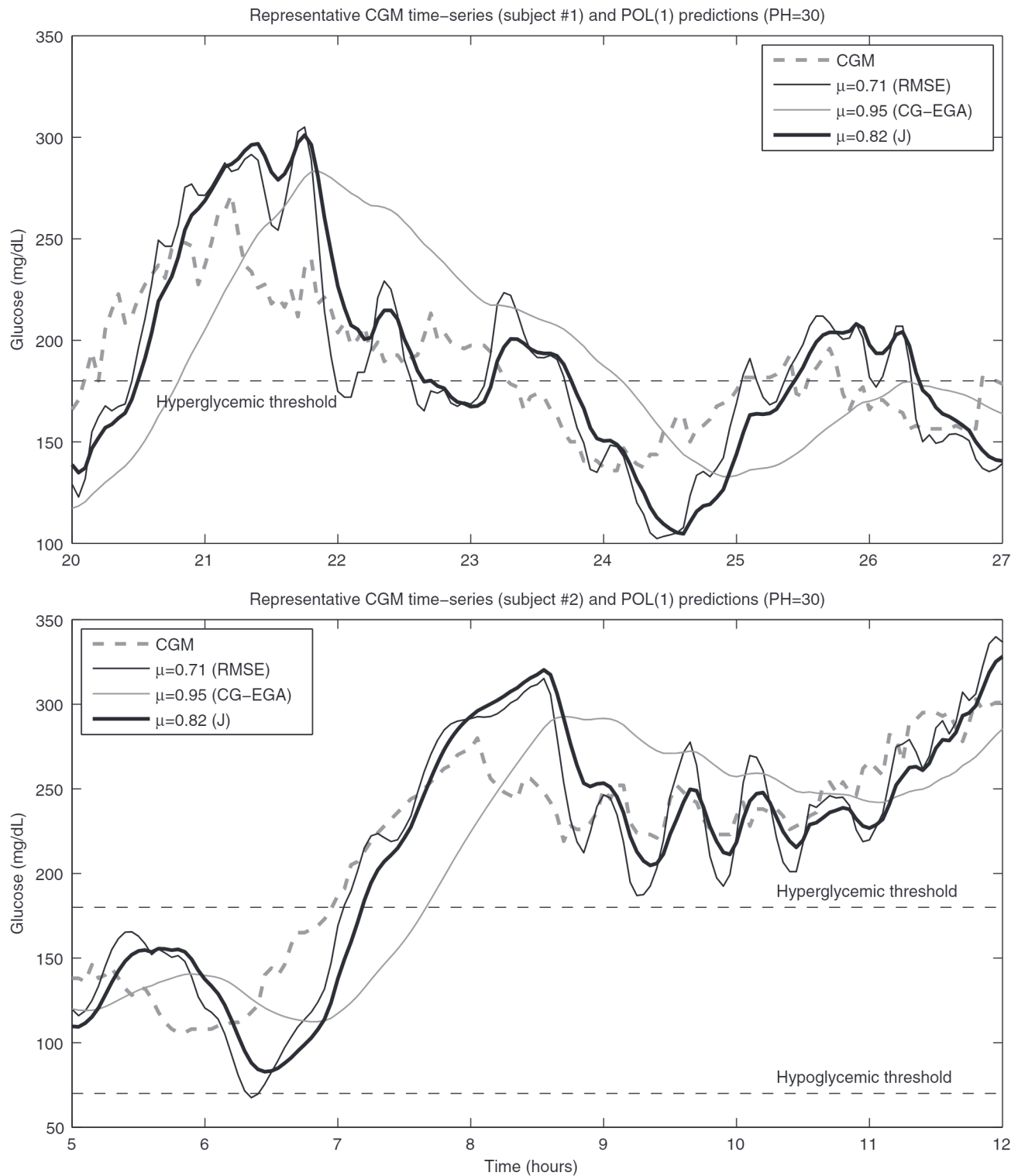


FIG. 3. (Top) Detail of the time window 20–27 h in representative subject #1 showing original continuous glucose monitoring (CGM) data (gray dashed line) and first-order polynomial POL(1) predicted time-series (prediction horizon [PH] = 30 min) obtained with forgetting factor (μ) equal to 0.71 (black thin), 0.95 (gray thin), and 0.82 (black thick). (Bottom) Detail of the time window 5–12 h of representative subject #2 showing original CGM data (gray dashed line) and POL(1) predicted time-series obtained with μ equal to 0.71 (black thin), 0.95 (gray thin), and 0.82 (black thick). CG-EGA, continuous glucose-error grid analysis; J, new index; RMSE, root mean square error.

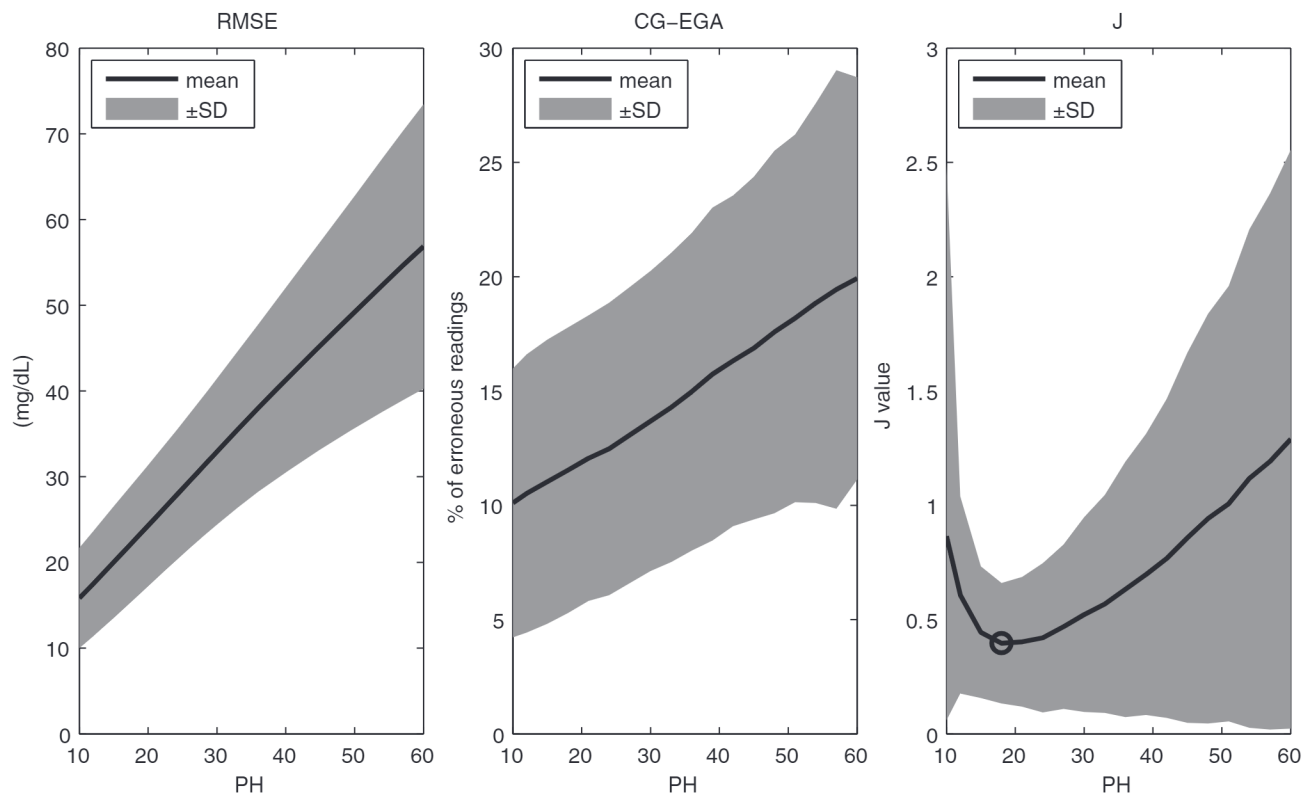


FIG. 4. Average ($\pm$ SD) values in the 20 subjects of root mean square error (RMSE) (**left**), percentage of erroneous readings in continuous glucose-error grid analysis (CG-EGA) (**middle**), and new index J (**right**) as function of prediction horizon (PH), respectively. The circle denotes the minimum value (detected only by J, right panel).

identification of a satisfactory compromise in determining their trade-off.

In order to better show the superiority of J over RMSE and CG-EGA for the determination of the optimal parameter set of a prediction algorithm, we have also investigated the performance of POL(1) in terms of prediction of hypo-/hyperglycemic events in all the 20 CGM time-series when μ is equal to 0.71 (as indicated by RMSE), 0.95 (as suggested by CG-EGA), and 0.82 (as obtained through J). Given the conceptual scope of the study, a hypo-/hyperglycemic event is defined simply by the crossing of the hypo-/hyperglycemic threshold. Considering all the subjects, the total number of hypoglycemic events is 74. The number of hypoglycemic alerts generated by the POL(1) prediction is 134, 61, and 97 when the value of μ is suggested by RMSE, CG-EGA, and J, respectively. This confirms that the parameter set suggested by RMSE results in a very large percentage of false alerts, whereas that indicated by CG-EGA leads to miss many hypoglycemic events. Using the parameter set indicated by J, the risk of generating false/missing true hypoglycemic alerts is significantly reduced. The same considerations can be drawn by repeating the procedure for the hyperglycemic episodes. In this case, in fact, in the presence of a total of 136 events, the number of alerts generated by the POL(1) prediction method is 220 (RMSE), 80 (CG-EGA), and 154 (J). Remarkably, the average TG in predicting hypo-/hyperglycemic events by POL(1) is 12, 0, and 10 min, using the parameter set suggested by RMSE, CG-EGA, and J, respectively. These results strengthen those previously displayed on the two representative subjects, i.e., J allows obtaining a TG

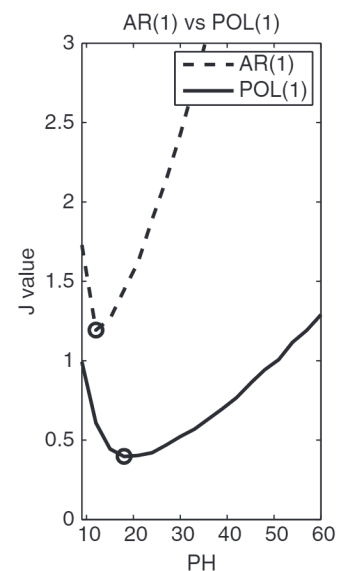


FIG. 5. Average values of new index J as a function of prediction horizon (PH) in the 20 subjects for first-order autoregressive model AR(1) (dashed line) and first-order polynomial POL(1) (continuous line). The circle denotes the minimum value.

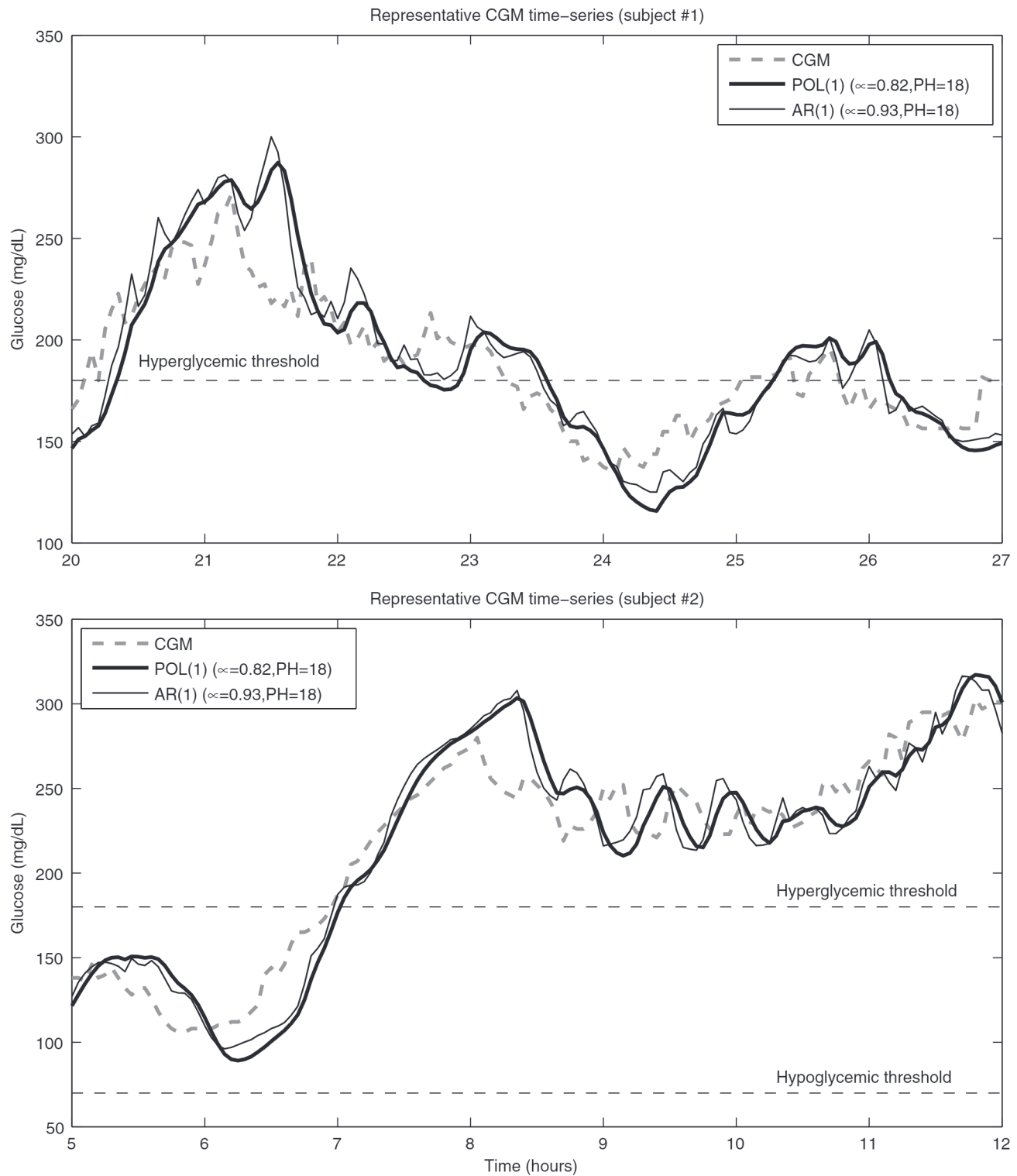


FIG. 6. Same representative subjects as in Figure 3 showing original continuous glucose monitoring (CGM) data (gray dashed line), first-order autoregressive model AR(1) prediction (black thin line) performed with prediction horizon (PH) = 18 min and forgetting factor (μ) = 0.93, and first-order polynomial POL(1) prediction (black thick line) performed with PH = 18 min and μ = 0.82.

very close to the one of RMSE but with a very limited number of false alerts (and no missing ones).

Remark 2. We report also a brief summary of individual results in the 20 subjects. The μ_{opt} average value (together

with the 10th and 90th percentiles) suggested by RMSE, CG-EGA, and J are 0.70 (0.49–0.84), 0.94 (0.87–0.99), and 0.83 (0.81–0.87), respectively. As one can note, whereas RMSE and CG-EGA under- and overestimate, respectively, the optimal value of μ and suggest for some subjects unreliable values

(e.g., 0.49 and 0.99), J is able to suggest reasonable parameter values for all subjects.

Choice of the optimal PH

Below we show that J can be used to find the optimal PH. Of note is that, in assessing the impact of PH in the prediction, we cannot fix the value of μ and let only PH vary because, as evidenced above, the prediction performance is strongly influenced by μ . Consequently, for each of the candidate PH tested, μ_{opt} is found as done in the previous paragraph according to the three criteria considered (RMSE, CG-EGA, and J). The prediction algorithm is the same POL(1) used above. We select different PH values, from a minimum of 9 to a maximum of 60 min, with the step equal to 3 min. For each PH and for each subject, the prediction obtained by POL(1) is determined by μ_{opt} suggested by each of the three indexes. Finally, for each PH, the average value of each index is computed together with the sample SD. Results are displayed in Figure 4, where average $\pm$ SD of RMSE, percentage of erroneous readings in the CG-EGA, and J are shown in the left, middle, and right panels, respectively. Both RMSE and percentage of erroneous readings in the CG-EGA increase with PH (left and middle panels), and none of these two indexes is able to suggest an optimal PH value. This is not unexpected because the higher PH, the greater the delay, and consequently the higher the distance between the two profiles measured by RMSE. On the other hand, concerning the CG-EGA, the higher PH, the greater the risk of predicting a clinical unacceptable value, and then the higher the number of erroneous readings. The behavior of J (right panel) is different, and a minimum is clearly evident. J reaches its lowest value in correspondence to PH = 18 min. Furthermore, the small variability around PH = 18 evidences that this PH value allows obtaining a satisfactory prediction for almost all the subjects.

In conclusion, we can affirm that only J is able to assess the optimal set for the prediction algorithm POL(1). In particular, for this specific dataset consisting of 20 subjects, the optimal set is given by $\mu = 0.82$ and PH = 18.

Comparison between different prediction algorithms

In order to conceptually show the possible utility of J in comparing different prediction algorithms, below we consider the POL(1) and AR(1) simple prediction strategies of Sparacino et al.⁸ and the same grid of PH values used in the previous section. For each PH and for each subject, the prediction is assessed by using the μ_{opt} suggested by J . Again, for each PH the average value of J is computed together with its population variability. The average J as function of PH for POL(1), already reported in Figure 4 (right), is displayed again in Figure 5 (continuous line) together with the profile obtained for the AR(1) prediction method (dashed line).

The shape of the J curve for AR(1) is qualitatively very similar to the one of POL(1) (black continuous line), and it exhibits a well-pronounced minimum in PH = 12 min. However, the average J profile for AR(1) is always higher than POL(1), suggesting that POL(1) performs better than AR(1). The graphical comparison of the predicted time-series obtained with the two methods confirms this result. Figure 6

shows, for the same representative subjects of Figure 3, the predicted profiles of AR(1) and POL(1) obtained applying a PH = 18 min. The μ_{opt} values are 0.93 and 0.82 for AR(1) and POL(1), respectively. AR(1) prediction (black thin line) anticipates the POL(1) curve (black thick line), as one can appreciate, e.g., in the rising fronts. In fact, the overall TG of AR(1) is higher than the POL(1) one (5 vs. 5 min and 8 vs. 6 min, respectively). However, obtaining a higher TG has a price in term of instability of the profile. In fact, AR(1) presents more unreliable oscillations than POL(1), e.g., in the time interval 20–22 h (top panel).

The J values for AR(1) and POL(1) are 1.63 and 0.33 for representative subject 1 and 2.27 and 0.58 for representative subject 2, meaning that the lower TG of the polynomial method is more than compensated for by the elevated regularity of its profile. This result has a clinical/practical interpretation and utility because it suggests that having up to 2 additional min of temporal gain would not be useful if the number of possible false alerts increases because of the higher irregularity of the predicted profile.

Conclusions

The ahead-of-time forecasting of glucose levels is important in order to prevent rather than simply detect critical events such as hypo- and hyperglycemia. In recent years, different prediction algorithms from CGM time-series have been proposed, but the comparison of their performance is difficult because of the lack of suitable metrics. At the same time, even focusing on a specific prediction method, the choice of the optimal parameter set is not trivial, and often it must be based on empirical criteria.

In this work we have proposed a new index, J , to optimally design a prediction algorithm by taking into account two key components: regularity of the predicted profile and time gained thanks to prediction. The effectiveness of J has been demonstrated on 20 real datasets, and its outcome has been compared with the ones coming from the use of previously proposed criteria such as RMSE and CG-EGA. Results showed that J is able to find the optimal set (μ and PH) better than RMSE and CG-EGA. Finally, we have proved that J can be used to compare the performance of different prediction strategies and to find the best one.

The particular data test bed and prediction algorithms should be viewed as a proof of concept in order to show the potentialities of J . In particular, the choice of considering only AR(1) and POL(1) was motivated by their simplicity and by the fact that both have the same parameters, i.e., μ and PH, to be set. Results in line with those reported here were observed also by using other sensors data, e.g., the Abbott (Alameda, CA) FreeStyle Navigator[®] and the DexCom[™] (San Diego, CA) Seven[®] (data not shown).

In conclusion, the new index J can be a useful and general tool for the design and development of prediction methods from CGM data aimed at the prevention of hypo-/hyperglycemic events.

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Author Disclosure Statement

The authors have no conflicts of interest.

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