Adaptive Calibration Algorithm for Plasma Glucose Estimation in Continuous Glucose Monitoring

Fatima Barcelo-Rico, Jose-Luis Diez, Paolo Rossetti, Josep Vehi, *Member, IEEE*, and Jorge Bondia

***Abstract*—Minimally or noninvasive continuous glucose monitors estimate plasma glucose from compartments alternative to blood, and may revolutionize the management of diabetes. However, the accuracy of current devices is still poor and it may partly depend on low performance of the implemented calibration algorithm. Here, a new adaptive calibration algorithm based on a population local-model-based intercompartmental glucose dynamic model is proposed. The novelty consists in the adaptation of data normalization parameters in real time to estimate and compensate patient's sensitivity variations. Adaptation is performed to minimize mean absolute relative deviation at the calibration points with a time window forgetting strategy. Four calibrations are used: preprandial and 1.5 h postprandial at two different meals. Two databases are used for validation: 1) a 9-h CGMS Gold (Medtronic, Northridge, USA) time series with paired reference glucose values from a clinical study in 17 subjects with type 1 diabetes; 2) data from 30 virtual patients (UVa simulator, Virginia, USA), where inter- and intrasubject variability of sensor's sensitivity were simulated. Results show how the adaptation of the normalization parameters improves the performance of the calibration algorithm since it counteracts sensor sensitivity variations. This improvement is more evident in one-week simulations.**

***Index Terms*—Artificial pancreas, calibration algorithm (CA), CGMS accuracy, type 1 diabetes.**

I. Introduction

ALTHOUGH results are not completely conclusive, many studies indicate that continuous glucose monitoring (CGM) contributes to a better and tighter glucose control in patients with type 1 diabetes [1]. Moreover, accurate and robust continuous glucose sensing is a "conditio sine qua non" for the development of the artificial pancreas. For this reason research on CGM is an increasing area of interest. However, the performance of current CGM devices has yet great margins of improvement [2], [3]. Indeed, regulatory agencies have authorized the use of CGM only as an adjunctive tool for diabetes management and not in substitution of intermittent capillary blood glucose measurements (SMBG), which still is the mainstay of home diabetes management.

A review of calibration algorithms (CA) used up to date for CGM can be found in [4]. Commercially available CGM devices use linear regression approaches [5], lacking the required accuracy especially in the hypoglycemic range. Several works [6], [7] have raised the hypothesis, either in small retrospective studies or in simulations, that the consideration of dynamic models (e.g., Kalman filters) may help improving accuracy.

In [8], a new CA for the improvement of CGM accuracy was presented. It was based on a set of weighted and added local models (LMs), having the advantage of describing local behaviors, when present, as compared to previous methodologies. For the proper identification and application of this new CA, a normalization of the inputs is required, as they might be of a different nature and magnitude. Population normalization (PN) parameters were used in this case, omitting the effects of patient-specific sensor sensitivity.

It is expected that the normalization of the electrical and glucose signals using individualized parameters significantly increases accuracy, since specific information of patient-to-sensor sensitivity will be included in the population model [7]. However, this requires an estimation of statistical properties of the sensor's current intensity and the glucose concentration signals for the patient when the resulting models are applied during real-time CGM operation.

To overcome this problem, an adaptive scheme is presented in this paper estimating new patient's normalization parameters in real time. Estimation is done through a minimization of the mean absolute relative deviation (MARD) at calibration points (capillary glucose) with a time window forgetting strategy. Four calibrations are daily used: preprandial and 1.5 h postprandial at two different meals. The method is validated with a retrospective clinical study and simulated data to emulate interpatient sensor variability and intrapatient sensitivity decay over seven days.

Results show how the adaptation of normalization parameters improves the performance of the CA with population parameters, since adaptation counteracts satisfactorily sensor sensitivity variations.

II. Methods

A. Principles of the Local-Model-Based CA

The CA is based on a dynamic model that describes the relationship between plasma glucose concentration and the signal from the sensor [9], which is representative of interstitial glucose (IG). A local-model-based (LMB) structure is considered

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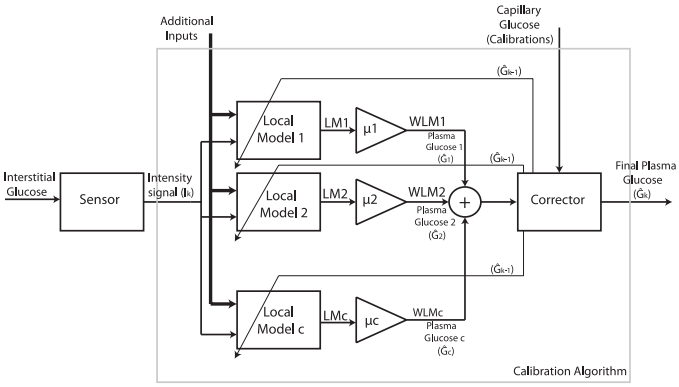

Fig. 1. Block diagram of the LMB CA.

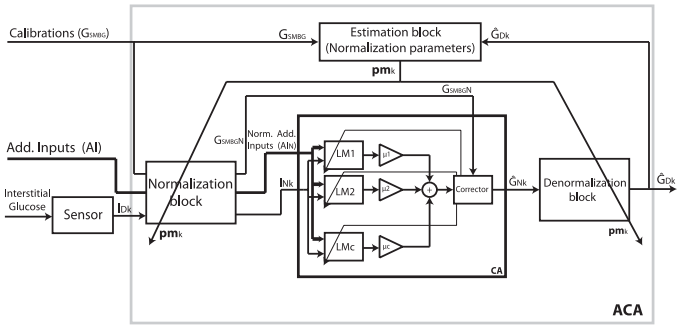

Fig. 2. Block diagram of the ACA.

to build this dynamic model, as described in detail in [10], where it was applied to general benchmarks. The application to CGM was first described in [8], where the CA in Fig. 1 was proposed.

An estimation of plasma glucose is computed from a weighted sum of local estimations given by a set of LMs obtained after data clusterization

$$\hat{G}(\vec{x}) = \sum_{i=1}^{c} WLM_i(\vec{x}) = \sum_{i=1}^{c} V_i(\vec{x}) \cdot LM_i(\vec{x}) \qquad (1)$$

where $\hat{G}$ is the plasma glucose estimation, $\vec{x} \in \mathbb{R}^d$ is the input vector composed of current and past values of sensor's current intensity and past glucose estimations (additional input signals may be considered in advanced configurations), c is the number of LMs (LM_i), and V_i: $\mathbb{R}^d \rightarrow [0, 1]$ are the validity functions describing the regions (clusters) represented by each LM. Each LM is independent and valid regionally, in order to obtain an interpretable global model (GM). The structure of each LM is chosen to be linear while the validity functions are chosen to be hypergaussian functions [11]. Then, the final equation of the model is

$$\hat{G}(\vec{x}) = \sum_{i=1}^{c} \left(e^{-\frac{1}{2}((\vec{x}-\vec{m}_{x_i})^T \Sigma_{x_i}^{-1} (\vec{x}-\vec{m}_{x_i}))^H} \times (\vec{\beta}_{1d_i} \vec{x} + \beta_{0_i}) \right). \qquad (2)$$

The resulting model is thus described by the following set of parameters: *regression coefficients* of the linear models ($\vec{\beta}_i := [\beta_{0_i} \ \vec{\beta}_{1d_i}]$), and *means* ($\vec{m}_{x_i}$) and *variances* ($\Sigma_{x_i}$) of the hypergaussian validity functions, all of them defined for each LM_i.

When the identified structure is applied, if the current input vector $\vec{x}$ is not highly represented by at least an LM (e.g., no LM exist with a validity degree higher than 0.85), the value of the estimation is set to the previous value, for its correct application.

Finally, glucose estimation given by the model is corrected every time a new calibration point (capillary glucose) is introduced, updating past values.

Local models (and their validity functions) need to be identified *a priori* from population data. Global optimization algorithms are used for the minimization of a cost index where global and local errors are considered. The reader is referred to [8] and [10] for the details.

The normalization strategy selected in this case makes variables 1) sensor's intensity signal and 2) plasma glucose concentration have null mean and unity variance. For this, mean and variance (m and σ^2) of original signals are required. Population (PN) or individualized (IN) normalization parameters can be used. Remark that in either case, population model parameters are considered, since a GM can describe better the dynamical behavior of the set of patients (with any normalization), and therefore it can be used for interpretation of results. In this case, it is well known that each sensor can have different sensitivity to changes in glucose concentration. Thus, IN is expected to perform better than PN since sensitivity information is included. Yet, the application of the CA after identification to a new patient is not possible since IN parameters for the new patient are not known beforehand.

B. Adaptive CA

A way to compute the individual parameters for inputs normalization is thus needed during CGM operation. Here, an adaptive algorithm is proposed to compute these parameters using information from the input and calibration points (SMBG). Thus, starting from population values, the parameters to normalize a new patient's data are progressively found online by minimizing the error between the estimated glucose output and the actual one known for the calibration samples (f_{error}). In this case, the function chosen to measure the error is the MARD which is a common measurement of the error in current monitors. The four parameters m_I, σ_I^2, m_G, and σ_G^2 are updated simultaneously considering them as a vector ($p\vec{m}_k$) defined at each time instant k.

Fig. 2 shows the block diagram of the adaptive calibration algorithm (ACA), where normalization/denormalization blocks are tuned in real time.

The technique used for this adaptation is the *steepest descent strategy* based on the gradient optimization techniques [12]. This is based on the computation of the gradient ($\partial f_{\text{error}}/\partial p\vec{m}$) at each iteration for a small change in the normalization parameters (positive and negative) and the posterior update of these parameters based on the direction where the objective function

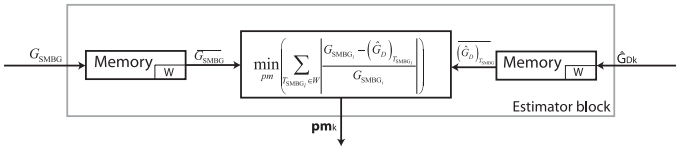

Fig. 3. Estimation block in the ACA.

is minimized

$$p\vec{m}_{k+1} = p\vec{m}_k - \alpha \cdot \frac{\partial f_{\text{error}}}{\partial p\vec{m}}. \tag{3}$$

Equation (3) shows how the adaptation depends on an additional parameter α which is the adaptation step and varies depending on the value of the gradient. This step and its adaptation thresholds are experimentally set such that it permits a fast convergence to the optimal parameters but not too large, as it would cause oscillations on the adapted parameters. In this case, the parameter starts at $\alpha = 0.001$. The more negative the $\Delta f_{\text{error}}/f_{\text{error}}$ (RelDF), the higher the α considered at discrete intervals, approximately doubling its value at each interval. An upper limit of $\alpha = 0.01$ is considered. For positive values of RelDF, α is reduced up to $\alpha = 1 \times 10^{-7}$, stopping adaptation.

On the other hand, to approximate the gradient the finite difference approximation is used

$$\frac{\partial f_{\text{error}}}{\partial p\vec{m}} \simeq \frac{f_{\text{error}}\left(p\vec{m}_k + \Delta p\vec{m}\right) - f_{\text{error}}\left(p\vec{m}_k - \Delta p\vec{m}\right)}{2\Delta pm} \tag{4}$$

where each component of (4) is computed by varying each parameter in $p\vec{m}$ independently by a magnitude Δpm.

Estimation of normalization parameters is only possible when reference information is available. Thus, every time a new calibration point is available, normalization parameters are updated according to (3), as depicted in Fig. 3. It is important to consider the influence of the sensor's sensitivity variations with time [13]. It is well known that sensor sensitivity is different for each patient, but also within the sensor's life time. Although the patterns of variation of sensitivity are not yet well known, a reduction of about 20–50% over time during the sensor's lifespan (six to seven days in current commercial CGM) has been reported [14], [15]: following a smooth increase of sensitivity during the first 24–48 h (as the postinsertion hemorrage is readsorbed [14]), there is a steep decrease due to the sensor fouling and other biological processes. Thus, the MARD will only be computed for a time window W including the last w calibration points, in order to estimate $p\vec{m}$ that best fits to the sensor sensitivity of a specific time interval. Thus, the final cost function for adaptation is defined as

$$f_{\text{error}} = \frac{\sum_{T_{\text{SMBG}_i}\in W}\left|\frac{G_{\text{SMBG}_i}-(\hat{G}_D)_{T_{\text{SMBG}_i}}}{G_{\text{SMBG}_i}}\right|}{w} \tag{5}$$

where T_{SMBG_i} is the time instant of the ith calibration point, G_{SMBG_i} is the ith calibration point glucose value, and $\hat{G}_D$ is the denormalized plasma glucose estimation.

With this adaptive scheme, the population model identified with IN can be applied to a new patient. Remark that adaption is carried out only on normalization parameters, counteracting different sensor sensitivities, but the same population dynamics is considered for all patients. Furthermore, the sensor sensitivity variations over time can also be counteracted, reducing the deterioration of the model response. Convergence time to the optimal patient's parameters, computational constraints, and performance under suboptimal normalization parameters will be analyzed in Section III.

C. Datasets

Two datasets were used to validate the ACA.

1) Data From a Clinical Study: Seventeen patients with type 1 diabetes were recruited at Dr. Josep Trueta Hospital (Girona, Spain). Subjects' characteristics were (mean $\pm$ std): age (years) 26.8 $\pm$ 4.9; sex (F/M) 8/9; BMI 24.5 $\pm$ 3; HA1bc (%) 8.5 $\pm$ 2.3; and diabetes duration (years) 15 $\pm$ 5.5. Patients were asked to wear CGMS Gold (MiniMed CGMS MMT-7102; Medtronic, Northridge, CA, USA). The device, which uses a retrospective CA and provides plasma glucose estimates every 5 min, was calibrated with SMBG at least three times per day, following manufacturer's instructions.

Each patient underwent a 9-h in-hospital study, where plasma glucose was measured by means of a Glucose Analyzer II (Beckman Instruments, Brea, CA, USA). Samples were taken every 15 min for 2 h after each meal and every 30 min otherwise.

To perform the model identification, plasma glucose measurements were interpolated using a cubic method every 5 min (sample period of CGMS Gold readings). Thus, a total of 1719 paired points were obtained. Because plasma glucose and CGMS Gold readings were obtained at different times, CGMS Gold readings were interpolated to the gold standard reference time vector to match both vectors in time.

Some gold standard samples (14 samples in 5 patients) were incorrectly measured (spiky values below 40 mg/dL). In this case, they were interpolated with the other signal samples to avoid gold standard outliers.

2) In Silico Study: As data with simultaneous CGM and gold standard measurements for the sensor's lifetime are not available, the validation was complemented with an *in silico* study. To generate one week's data, the FDA-accepted UVa simulator was used [16]. CGM devices do not measure directly blood glucose (BG), but the sensor's current signal reflects IG, with variations of sensor sensitivity as already described. Since both IG and BG are available in the simulator, sensor's operation can be emulated.

The sensor sensitivity variations were reproduced following the model found in [7]. Among the diverse set of curves that follows this stochastic model, one that changes accordingly to the expected decay with time was chosen and scaled randomly per patient to have variations in the range [20, 50]%, as shown in Fig. 4.

To generate one-week data, IG signal coming from the simulator was converted to intensity (I) measurements ($I = S_i \cdot IG$), following these indications.

1) A different sensor sensitivity S_i was considered for each patient. This sensitivity was taken randomly in the range [0.09, 0.24], obtained from the ratio of the glucose gold

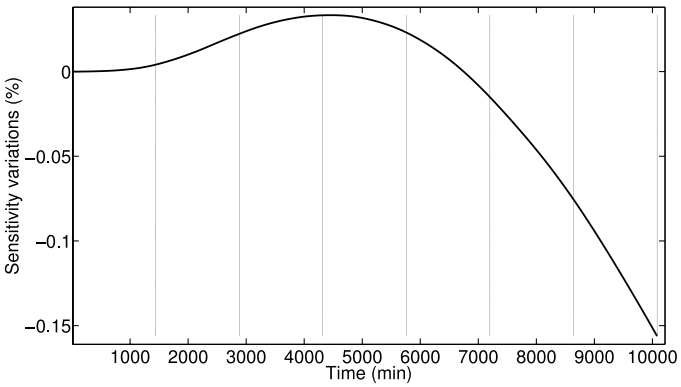

Fig. 4. Shape of the sensor sensitivity variation for seven days, for a 20% range.

standard and sensor's current intensity averages for the 17 patients of the previously described clinical study.

2) A degradation of this sensitivity was considered following the perturbations shown in Fig. 4 and scaled randomly for each patient within the range [20, 50]% for each patient.

Thirty patients (adults) were considered for this *in silico* study, generated from the ten adults available in the educational version of the simulator and the procedure described previously to assign the sensor's sensitivity (every patient was studied three times with "different sensors"). A period of one week was simulated with three meals per day: breakfast (7 A.M.), lunch (12 P.M.), and dinner (18 P.M.). The meals were similar for all patients and days, with variations up to 40%. Four calibrations were considered per day (preprandial and 1.5 h postprandial for breakfast and dinner). To emulate glucometer accuracy, a variation of $\pm 10\%$ (uniform distribution) was introduced to the BG samples generated by the simulator.

D. Validation Tests

The following validation tests were performed.

1) Performance of the IN and the adaptive scheme against CGMS Gold from the clinical database. A leave-one-patient-out-cross-validation was carried out. Population LMs were identified for the set of patients except one, and the CA was applied to this one to check its performance. This was repeated so that every patient was included once into the validation set. This is equivalent to k-fold cross-validation with k equal to the number of patients.
2) Performance of the IN and the adaptive scheme from *in silico* data. In this case, population LMs were identified for the whole set of patients considering the data from the first day. The algorithm was then validated on different data from days 2 to 7 subjected to sensor sensitivity variations.
3) Additional experiments were run in the *in silico* study to check the performance of the ACA under different situations.
   a) First of all a convergence study was carried out, as well as the performance analysis under a limitation of the computation time (suboptimality condition).
   b) Second, performance under measurement noise in the intensity signal was checked.
   c) Finally, a comparison of the performance of several calibration strategies including deviations in timing and missing data was done.

ISO criteria[1] and MARD were computed for the overall and hypoglycemia ranges as performance indicators. In all cases, the statistical analysis of the results was performed with ANOVA for repeated measures with Bonferroni adjustments for *post hoc* comparisons.

E. Further Considerations

Henceforth, I will refer to current intensity signal while G refers to glucose in plasma. $\hat{G}$ refers to the glucose estimation of the GM. Subindex i refers to the ith LM, k is the kth time sample, and c refers to the number of LMs. Finally, the suffix N will refer to normalized signals I_N, G_N, and $\hat{G}_N$. The parameters of the model (and LMs) were already described in Section II-A.

As the model is recursive, a calibration is needed at the beginning of the computation. Thus, at time $k = 1$ $\hat{G}_0$ was replaced by G_0. As clinical data available for each patient vary between 7 and 9 h, it makes sense to introduce another calibration, as usually patients take a calibration every 6 h. This calibration was introduced for all patients just before dinner (7 P.M.) where all of them have a point from the glucometer. As this point was taken at equilibrium conditions, the differences between this measurement and BG were minimal.

III. Results

A. Clinical Study

1) Individual Normalization: The model identified in [8] was not directly applicable to the clinical study data, since PN was used there. Besides, healthy subjects were studied. However, the model structure identified in [8] ($\vec{x} = [I_{Nk}\ I_{Nk-1}\ \hat{G}_{Nk-1}]$, abbreviated as IIG) was considered as the starting point in this study for the identification of the IN model. Other structures (increasing the order of *I* and/or *G* signals) were checked, yet results did not reveal significant differences. For this reason, according to the parsimonious principle, the IIG structure was chosen.

Table I, columns N1 and N2, shows the performance of the IN model for $c = 2$ and $c = 1$, respectively, for a leave-one-out cross-validation, considering IN parameters for the patient in the validation set are known. Remark that this is an ideal condition and results obtained are a "best-case performance" for these data. A paired t-test between N1 and N2 showed no significant difference ($p = 0.23$). Some overmodeling seems to appear with $c = 2$ in these data. If the histogram of sensor's sensitivity is studied in dataset 1 and compared with the Gluco-day 3-h clamp data used in [8] (see Fig. 5), distributions with different modalities are obtained. This may explain the better performance of just one LM with the CGMS Gold, as compared

[1]ISO criteria for glucose estimations defines that a measurement is correct if the difference with the reference value (Gr) is smaller than 15 mg/dL for values under 75 mg/dL or smaller than 20% for Gr over 75 mg/dL.

TABLE I
RESULTS: % OF WELL-ESTIMATED SAMPLES ACCORDING TO ISO CRITERIA AND MARD, BOTH FOR THE WHOLE AND HYPOGLYCEMIC RANGES

	CASES				
	CGMS Gold	**N1**	**N2**	**M1**	**p value**
	All range				
ISO (%)	77.4 (14.58)	87.14† (16.69)	89.06† (14.82)	78.13 (13.77)	0.008
MARD (%)	15.1 (5.43)	11.59 (10.7)	9.82 (4.09)	12.72 (4.22)	0.12
	Hypoglycemic range				
ISO (%)	71.9 (28.09)	89.71 (12.99)	92.21 (13.9)	85.07 (29.3)	0.13
MARD (%)	21.6 (16.62)	12.33 (4.67)	11.7 (4.56)	14.67 (13.22)	0.09

Mean (standard deviation). Case N1 is the IIG structure, with c=2 and known individual normalization (IN). Case N2 is the IIG structure with c=1 and known IN. Case M1 is IIG structure with c=1, plus the adaptive scheme (ACA with four calibrations) for the unknown IN. †p<0.05 versus CGMS Gold.

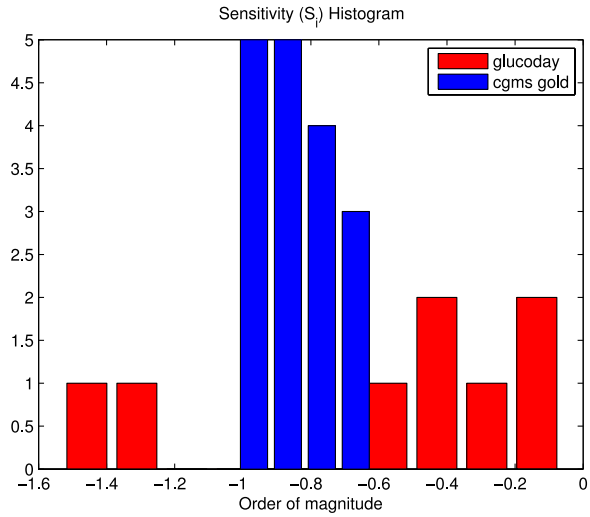

Fig. 5. Histogram of order of magnitude of sensor's sensitivity for Glucoday (bimodal) and CGMS Gold (unimodal).

to previous results with the Glucoday device. However, data are not rich enough for conclusive results and further studies should be carried out to check this fact.

For this reason, in this study just one LM will be considered (plus its validity function) for further studies.

2) Adaptive Calibration Algorithm: This refers to the application of the identified model for IN to a new patient, where the vector of normalization parameters $p\vec{m}$ is unknown. $p\vec{m}$ was initialized using the mean of the individual parameters of the population used for the identification of the model, according to a leave-one-out cross-validation. After initialization, parameters were adapted to minimize the difference of the glucose estimation and the reference measurements (calibrations). It is important to mention that although the optimization is done using only calibration points, the performance has to be tested on the full set of gold standard data.

Several studies were carried out using different calibration strategies and different number of calibrations. All calibration strategies employed a realistic number of calibrations (3–4 per day). Finally, the one with best results and feasibility for the patients was to use a total of four calibrations per day, plus an initial calibration for the algorithm (for the start-up). The four calibrations were taken at preprandial (just before they eat) and 1.5 h postprandial times for lunch and dinner. Finally, 15 patients were considered, as two patients did not have information for lunch time. The structure considered here was IIG with just one LM, column N2 in Table I. Results are shown in Table I, column M1. The time allowed for the optimization was 10 s between samples for a processor running at 2.67 GHz, which is equivalent to 5 min in a conventional 100 MHz microprocessor.

For case M1, in addition to MARD and ISO measures, the continuous glucose error grid analysis [17] was also computed. For the overall range, 92.18% of the samples were accurate readings, 4.61% were benign errors, and only 3.21% were erroneous estimations. For the original monitor, the results were, respectively, 93.09%, 2.26%, and 4.65% (large number of erroneous readings). Graphical results are depicted in Fig. 6. Since the ISO criteria is more restrictive (78.13% versus 92.18% for our algorithm), in next case studies, only the ISO and the MARD will be considered for performance evaluation.

As an illustration, Fig. 7 shows the glucose output profile of the ACA as compared to reference glucose and CGMS Gold for Patient 3.

B. In Silico Study

1) Adaptive Calibration Algorithm: The clinical data available consist of around 9 h per patient, and the full performance of the adaptive scheme cannot be tested. For this reason, the proposed ACA was fully tested with one-week *in silico* data and a larger population of 30 patients.

The use of longer time data allows us to check different aspects of the algorithm: first, convergence of the parameters and second, the performance in face of the variations of sensitivity over time.

The model structure applied was the same as in the clinical data case, i.e., IN, IIG structure and $c = 1$, Table II column Y1. The population model identified for the first day was tested the following days (2 to 7), emulating CGM operation. Four calibrations were made per day, at preprandial and 1.5 h postprandial times for breakfast and dinner, plus an extra calibration for the first day for the start-up of the algorithm. The time allowed for the optimization was 1 s between samples, which in a processor running at 2.67 GHz is equivalent to 5 min in a conventional 10 MHz microprocessor. A window of four calibrations ($w = 4$), corresponding to one day, was considered to do the optimization for the parameters' adaptation, according to (5), since the studies of different w showed that this was the window's length with best performance.

Table II shows the results for the adaptation algorithm (column Y2). Results are compared with the application of the identified model when no adaptation of parameters is done, column Y3. Performance is drastically improved with adaptation, both for ISO and MARD in the whole glucose range and hypoglycemia, with statistical significance.

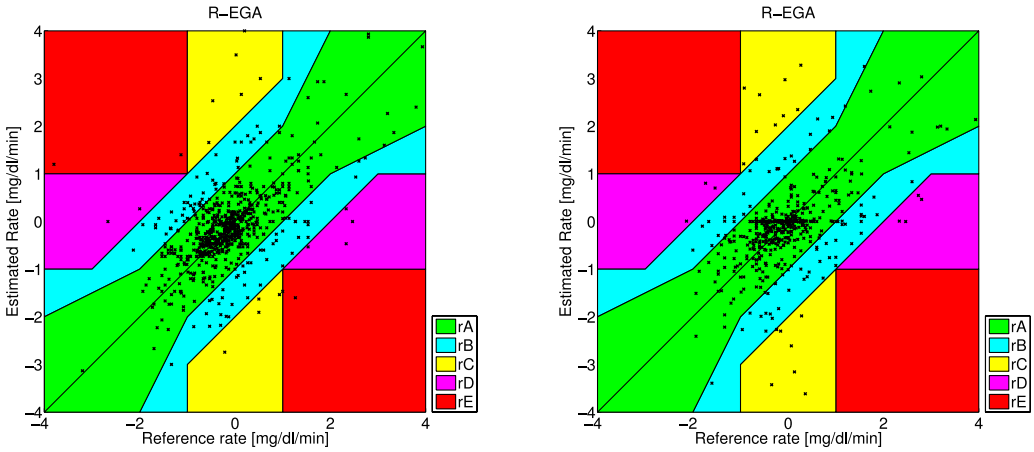

Fig. 6. (Left) comparison of rate-EGA (R-EGA) graphics for the original monitor used and (right) proposed ACA algorithm for its basic configuration, case M1.

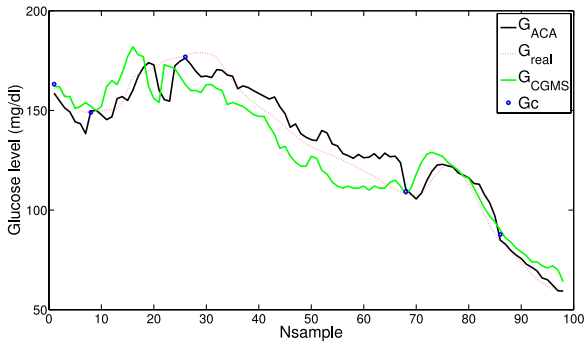

Fig. 7. Estimation samples of glucose (black line) using the ACA with four calibrations (blue) for Patient 3. Comparison with reference glucose (red-dotted) and estimations from CGMS Gold (green). Each sample is synchronized with CGMS (5 min).

TABLE II
RESULTS: % OF WELL-ESTIMATED SAMPLES ACCORDING TO ISO CRITERIA AND MARD, BOTH FOR THE WHOLE AND HYPOGLYCEMIC RANGES

	Identification	Validation		
	Y1	**Y2**	**Y3**	p
	All range			
ISO (%)	99.97 (0.11)	90.61 (7.94)	60.28 (27.7)	< 0.0001
MARD (%)	1.76 (0.44)	9.13 (2.8)	18.73 (9.03)	< 0.0001
	Hypoglycemic range			
ISO (%)	100 (0)	87.55 (11.93)	63.38 (27.44)	0.042
MARD (%)	1.27 (0.13)	13.11 (4)	17.66 (7.28)	0.038

Mean (standard deviation). All results are for 30 patients. Case Y1 is the model indentification's results for IIG structure with c=1 and known individual normalization (IN). Case Y2 is the application of identified Y1 to days 2 to 7 with adaptive scheme. Case Y3 is the application of Y1 to days 2 to 7 with no parameters' adaptation. Identification results Y1 are not considered for the ANOVA test.

Fig. 8 shows the comparison of the one-week performance of both estimations for a sample patient.

2) Convergence and Suboptimal Performance: Additional *in silico* experiments were performed to study the robustness of the ACA. In the first place, the parameter's convergence was studied and it was found that the optimum value was not reached for some patients. For this reason, a study of the performance of the ACA when the computation time is limited (suboptimality conditions) was carried out. Indeed, power management in commercial monitors constrains the available computation time in such adaptive schemes. Table III shows in columns Z1 and Z2 the performance when the computation time is limited to one and four samples (5 and 20 min), respectively, from the time a new calibration is performed, with a processor of 10 MHz. Column Z3 shows the performance when computation time is limited to just one sample (5 min) after a calibration, with a microprocessor of 100 MHz. Z1 showed a statistically significant degradation of performance. For the rest of configurations, Z2 and Z3, no statistical difference was found with the unconstrained case Y2. Thus, even under suboptimality, the adaptation is feasible. Based on these results, the next experiments were done under the configuration Z3.

3) Noisy Current Intensity Measurements: To check the robustness of this algorithm, two aspects were checked. One was the introduction of some noise in the current measurements. To see a realistic value for this noise, a frequency study of the current signals of the CGMS Gold monitor was performed. After filtering the low frequencies, a noise signal remained with an amplitude between 3% and 8%. For this reason, a random noise of 5% was incorporated to the I signal. Performance of the application of the model identified for day 1 with the adaptive scheme to the rest of the days (2 to 7) is shown in column V1.

4) Calibration Strategy Including Deviations in Timing and Missing Data: The second aspect to check the robustness of the ACA is to modify the calibration strategy used. Several cases were studied, as shown in Table V, trying to represent different realistic scenarios. The requirements of this system is to have between three and four calibrations per day, in pre- and postpandrial times. Results show that some missing postpandrial calibrations or the modification of the time of calibration do not imply a significant degradation of the performance of this algorithm.

IV. DISCUSSION

Results in Table I, columns N1 and N2, show a clear performance improvement of the IN method with respect to the CGMS

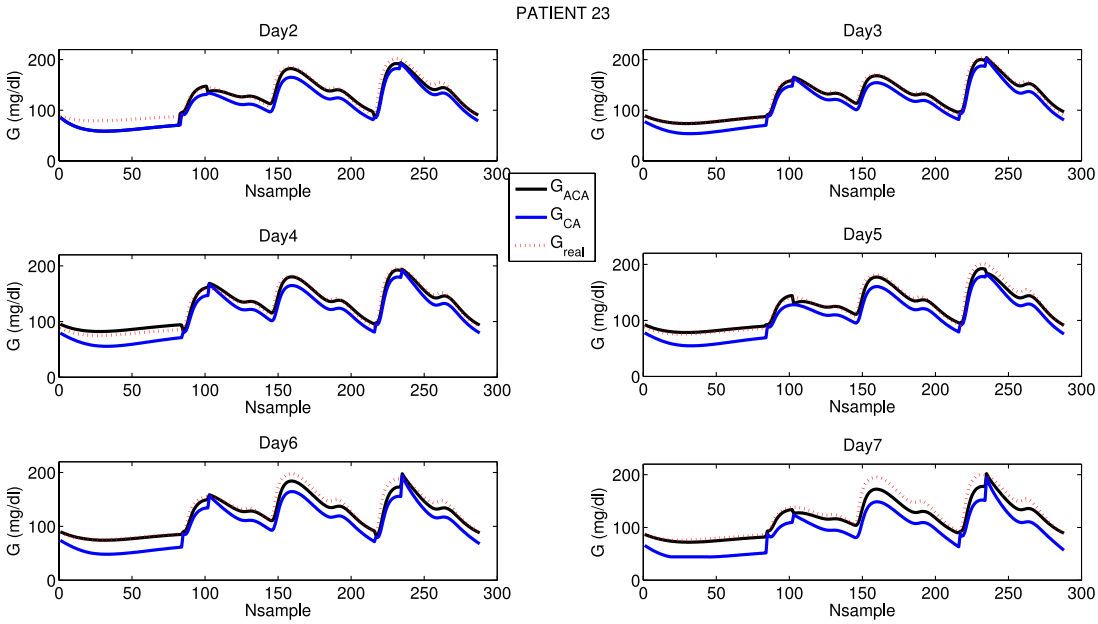

Fig. 8. Estimation of samples of glucose (black line) using the ACA with four calibrations and $w = 4$ for Patient 23. Comparison with reference glucose (red-dotted) and nonadaptive CA (blue). Each sample is synchronized with CGMS (5 min).

TABLE III
RESULTS: % OF WELL-ESTIMATED SAMPLES ACCORDING TO ISO CRITERIA AND MARD, BOTH FOR THE WHOLE AND HYPOGLYCEMIC RANGES

	Reference	CASES			
	Y2	**Z1**	**Z2**	**Z3**	p
	All range				
ISO (%)	90.61 (7.94)	85.56† (14.44)	88.76 (9.92)	89.59 (9.38)	0.03
MARD (%)	9.13 (2.8)	10.45† (3.99)	9.59 (3.06)	9.35 (2.92)	0.0013
	Hypoglycemic range				
ISO (%)	87.55 (11.93)	87.82 (10.51)	88.34 (10.47)	88.26 (10.39)	0.24
MARD (%)	13.11 (4)	12.86 (3.72)	12.79 (3.69)	12.71 (3.66)	0.17

Mean (standard deviation). All results are for 30 patients. Case Z1 is the ACA when computation time is limited to 5 min (one sample) with 10 MHz microprocessor. Case Z2 is the same as Z1 with a limitation of 20 min (four samples). Case Z3 is the same as Z1 but with 100 MHz microprocessor. †p<0.05 versus reference Y2.

TABLE IV
RESULTS: % OF WELL-ESTIMATED SAMPLES ACCORDING TO ISO CRITERIA AND MARD, BOTH FOR THE WHOLE AND HYPOGLYCEMIC RANGES

	Reference	Noisy meas.	
	Z3	**V1**	p
	All range		
ISO (%)	89.59 (9.38)	90.31 (7.16)	0.32
MARD (%)	9.35 (2.92)	9.4 (2.51)	0.79
	Hypoglycemic range		
ISO (%)	88.26 (10.39)	85.37 (11.02)	0.012
MARD (%)	12.71 (3.66)	13.02 (3.29)	0.53

Mean (standard deviation). All results are for 30 patients. Case V1 is application to days 2 to 7 with parameters' adaptation of the identified model for day 1 with IN when a noise of 5% is introduced in the current signal.

Gold[2] (statistically significant for the whole glycemic range). This confirms the influence of interpatient sensor variability. Contrary to Glucoday clamp data in [8], no significant difference was found between $c = 2$ and $c = 1$. This is suspected to be due, as already stated, to the unimodal distribution of sensor's sensitivities in CGMS Gold data as compared to Glucoday. However, more clinical studies are needed to get conclusive results. For $c = 1$, a MARD below 10% is obtained when the whole glycemic range is considered, reaching a MARD reduction of about 35% with respect to the CGMS Gold. Regarding the hypoglycemic range, the improvement is even better, with a MARD reduction of 46% reaching values of about 11.7%. This was expected, as interpatient sensitivity variations were compensated by individualizing the normalization parameters, eliminating thus a confounder of the dynamics between compartments. But this case is ideal, since IN parameters are considered to be known. Thus, this performance is not attainable in practice and it must be considered as an upper limit of what can be achieved.

When the ACA is applied to IN parameters, improvement can still be observed as shown in Table I, column M1. The clear limitation of the clinical data used due to its short duration and scarcity of capillary measurements to carry out the adaptation must be taken into account. Nevertheless, the adaptive scheme manages to decrement the MARD about 2.3% (16% reduction with respect to CGMS Gold) during the first day and four calibrations per patient. Improvement is more evident in the hypoglycemic range, with a reduction of around 32% in the MARD, depending on the model considered. Obviously, with

[2]For the clinical study, the monitor used by the patients is chosen as reference to compare the performance of the proposed algorithms since this measure can be analyzed objectively with no need of implementing other CA which sometimes are not feasible due to the data used in a new study.

TABLE V
RESULTS: % OF WELL-ESTIMATED SAMPLES ACCORDING TO ISO CRITERIA AND MARD, BOTH FOR THE WHOLE AND HYPOGLYCEMIC RANGES

	Ref.	CASES					
	Z3	**R1**	**R2**	**R3**	**R4**	**R5**	p
	All range						
ISO (%)	89.59 (9.38)	90.46 (7.86)	90.56 (9.07)	89.64 (9.43)	89.73 (8.77)	89.94 (8.4)	0.17
MARD (%)	9.35 (2.92)	9.37 (2.67)	9.08 (2.9)	9.47 (3.04)	9.25 (2.72)	9.25 (2.71)	0.34
	Hypoglycemic range						
ISO (%)	88.26 (10.39)	86.58 (11.13)	86.03 (10.91)	90.93 (7.29)	87.16 (11.09)	87.31 (10.91)	0.12
MARD (%)	12.71 (3.66)	12.92 (3.24)	13.08 (3.54)	12.15† (3.19)	12.91 (3.69)	12.93 (3.68)	0.005

Mean (standard deviation). All results are for 30 patients. Modification of calibration strategies. Case R1 is the consideration of three premeal calibrations. Case R2 is consideration of two preprandial and two postprandial (2PP) calibrations randomly at 1.5h±0.5h. Case R3 is the consideration of 2PP calibrations with three postprandial calibrations randomly missing per week (same ones for all patients). Case R4 is the consideration of 2PP calibrations with one postbreakfast calibration missing per week (different days for different patients). Case R5 is the same as R4 but the missing calibration is postdinner. $^{\dagger}p<0.05$ versus reference Z3.

just four calibrations it is difficult to converge to the optimal parameters and statistical significance was not reached. However, this result points out that with availability of longer time data, this adaptation would reach a more significant reduction in the MARD, getting closer to N2. This justifies the *in silico* studies performed for a full validation of the ACA performance.

For the one-week *in silico* data the identified model has good performance during the first day (identification day), as shown in Table II, column Y1. It must be considered that the use of simulated patients makes much easier the identification task, reaching MARD values of 1.76% which obviously must not be expected with real data. The performance of the ACA, column Y2, versus the application of the CA with no adaptation, column Y3, improves when both CAs are applied for the rest of the days (days 2–7). A reduction in the MARD of 51% is achieved when adaptation is considered, as compared to no adaptation, for the whole glycemic range. In the case of hypoglycemia, the reduction reaches 26%.

Thus, results obtained with one-week *in silico* data indicate, as well as the validation case with clinical data, that the ACA is capable of compensating sensor's sensitivity variations (inter- and intrapatient), as new information is considered for the adaptation of normalization parameters allowing for the model adjustment to the new patient characteristics. Statistical significance was achieved in these results; see Table II.

It is important to mention that only 9 of the 30 *in silico* patients present hypoglycemic events (results from randomly simulated patients). This makes this population small to lead to any conclusive analysis in this region in the statistical tests.

When power management issues are taken into account and computation time is limited to just one sample interval (5 min) with a 100-MHz microprocessor, or four samples interval (20 min) with a 10-MHz microprocessor, results show that the performance of ACA is similar to the unconstrained case. This indicates that the proposed algorithm meets commercial requirements for its implementation. Results are significantly different when all cases are considered. This is due to the degradation of results when the 10-MHz microprocessor is used and only one iteration after calibration is allowed for computation, which is the most restrictive case. If the other two cases (Z2 and Z3) are considered and compared to the "ideal" case Y2, no significant differences are found.

In addition, when some perturbations with regard to the original configuration are introduced (noise in the sensor's measurement), the proposed algorithms still performs well; see Table IV. This shows the robustness of the algorithm with expected and possible changes in its daily application. Significant differences are only present in the ISO criteria for the hypoglycemic region, probably due to the small size of the population.

If different calibration strategies are tested (see Table V), results are very similar to the reference case Z3, even when deviations from the calibration timing or missing calibrations are present. Results do not present significant differences in the overall range. Only in the MARD of the hypoglycemic region results differ significantly. Paired *t*-test between the reference case and each calibration strategy indicates that the MARD in this region is better for case R3. This makes sense since when three postmeal calibrations are not introduced, less information of hyperglycemia is considered and better estimation of the hypoglycemic region is expected due to nonlinearities.

V. CONCLUSION

In conclusion, the performance of current CGM devices can be improved with the incorporation of interstitial-plasma glucose dynamics into the CA and adaptation of normalization parameters, reaching a significant increase in CGM accuracy. This is so even in the hypoglycemic range, where the lack of accuracy is an evident problem. The promising results obtained motivate further clinical studies with larger populations.

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