Real-Time Improvement of Continuous Glucose Monitoring Accuracy

The smart sensor concept

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OBJECTIVE—Reliability of continuous glucose monitoring (CGM) sensors is key in several applications. In this work we demonstrate that real-time algorithms can render CGM sensors smarter by reducing their uncertainty and inaccuracy and improving their ability to alert for hypo- and hyperglycemic events.

RESEARCH DESIGN AND METHODS—The smart CGM (sCGM) sensor concept consists of a commercial CGM sensor whose output enters three software modules, able to work in real time, for denoising, enhancement, and prediction. These three software modules were recently presented in the CGM literature, and here we apply them to the Dexcom SEVEN Plus continuous glucose monitor. We assessed the performance of the sCGM on data collected in two trials, each containing 12 patients with type 1 diabetes.

RESULTS—The denoising module improves the smoothness of the CGM time series by an average of ~57%, the enhancement module reduces the mean absolute relative difference from 15.1 to 10.3%, increases by 12.6% the pairs of values falling in the A-zone of the Clarke error grid, and finally, the prediction module forecasts hypo- and hyperglycemic events an average of 14 min ahead of time.

CONCLUSIONS—We have introduced and implemented the sCGM sensor concept. Analysis of data from 24 patients demonstrates that incorporation of suitable real-time signal processing algorithms for denoising, enhancement, and prediction can significantly improve the performance of CGM applications. This can be of great clinical impact for hypo- and hyperglycemic alert generation as well in artificial pancreas devices.

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Continuous glucose monitoring (CGM) technology has significantly modified the way glucose levels are monitored in patients with type 1 diabetes, allowing an increase in the number of readings from, for example, 3 to 4 spot measurements per day to a continuous glucose signal (1,2). In the beginning, CGM was used retrospectively to analyze glycemic profiles and to better understand glucose variability (3). Then, thanks to advances in technology, CGM systems turned into real-time devices, and their benefit in improved glycemic control and reduced risks of hypo- and hyperglycemia became evident (4–6).

The large amount of data obtained by CGM sensors stimulated the development of several applications. The most straightforward application is to combine CGM with a system for real-time generation of alerts when the measured glucose value crosses hypoglycemic (e.g., 70 mg/dL) or hyperglycemic (e.g., 180 mg/dL) thresholds (7). Another possible use is within systems that combine a CGM and a continuous subcutaneous insulin infusion pump in a single unit, the so-called sensor-augmented pump, whose use can produce a reduction of hyperglycemia and an improvement in glycemic control (8–10). Among all, the most ambitious is probably the artificial pancreas (AP), a system for delivering insulin steered by a closed-loop control algorithm in which the uncertainty and accuracy of the CGM sensor play a crucial role because the CGM measurements feed the control algorithm (11).

Even if the reliability of CGM outcome in accuracy is key, CGM performance is still suboptimal because of three main issues (12,13) that are related more to the way in which the stream of data given in output by the sensor is processed rather than on the electrochemical processes occurring within the sensor. The first issue is related to the uncertainty of CGM data, because glucose readings are corrupted by random noise that complicates their interpretation and use (14,15). For instance, noise may result in spurious spikes and oscillations that could trigger false hypo- or hyperglycemic alerts. Some denoising algorithms have recently been developed to deal with this problem (14–17).

The second issue concerns accuracy. In fact, compared with gold standard blood glucose (BG) references measured by laboratory instruments, the CGM time series present delays, which are mainly due to the blood-to-interstitium glucose transport and the sensor processing time (18), and often systematic under- or overestimations due to calibration problems (19–21). For instance, when actual glucose is in the hypoglycemic range, systematic overestimation of glucose levels due to lack of calibration can expose the patient to critical situations. To compensate for the inaccuracy and to enhance CGM data, several strategies have been proposed in the last few years (20–25).

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Finally, because CGM sensors report glucose value with a delay with respect to BG, there is the necessity of generating hypo- and hyperglycemic prealerts by applying short-term glucose prediction strategies (26–32). Generation of prealerts can allow the patient to take prompt countermeasures before a forthcoming (e.g., hypoglycemic) event, increasing the possibility of mitigating or even avoiding, it.

So far, these mentioned methods have always been tested in the literature as stand-alone applications, and a quantification of the improvement in CGM performance that can be achieved by their combination has never been assessed. Therefore, we propose the concept of a smart CGM (sCGM) sensor consisting of a cascade of a commercial CGM sensor and three software modules for denoising, enhancement, and prediction, able to work in real time.

RESEARCH DESIGN AND METHODS

Database

The sCGM sensor was tested on two databases collected within the AP@home European Commission's Framework Programme 7 (FP7-EU) project (33) in four clinical research centers (CRC) of the consortium: Academic Medical Center Amsterdam (Amsterdam, the Netherlands), Medical University of Graz (Graz, Austria), Profil Institute for Metabolic Research GmbH (Neuss, Germany), and Department of Clinical and Experimental Medicine, University of Padova (Padova, Italy).

The first database, hereafter labeled as study 1, consists of 12 subjects (7 men, 5 women) with type 1 diabetes. Inclusion criteria were age ≥18 years, type 1 diabetes diagnosed for >6 months, BMI <35 kg/m^2, insulin therapy by using an insulin pump for at least 3 months, and HbA_{1c} <10%. Mean ± SD demographic information is age, 45.3 ± 14.8 years; duration of type 1 diabetes, 19.0 ± 8.2 years; HbA_{1c}, 62.0 ± 9.4 mmol/mol; and BMI, 25.1 ± 2.6 kg/m^2.

The protocol of study 1 was specifically assigned to assess CGM sensor performance and consisted in a 7-day observation period. Each participant wore two Dexcom SEVEN Plus (Dexcom, Inc., San Diego, CA) CGM sensors in parallel. Sensor insertion and removal was performed at the CRC. The first CGM sensor (hereafter labeled as 1) was calibrated immediately after insertion and then every 48 h (~0630 h), the second CGM sensor (hereafter labeled as 2) was calibrated according to the manufacturer's instructions (i.e., once every 12 h). At ~1630 h of day 3, patients were admitted to the CRC for 24 h. During this period, BG samples were collected for glucose measurements (YSI 2300, Yellow Springs Instruments, Yellow Springs, OH) every 15 min from the beginning of a meal until 3 h after and every 2 h in the other periods. During the 24 h spent in the CRC, the patient was able to walk around between sampling of blood.

In study 1, the architecture for the sCGM sensor was applied to the CGM sensor 1 of each patient. The calibration schedule of this sensor was designed in such a way (every 48 h) that the number of built-in calibrations that could interfere with the enhancement module was limited. This allowed us to test the sCGM sensor algorithms in optimal conditions. We used CGM sensor 2 for comparisons, and by wearing two sensors, each patient served as his or her own control.

The second database, hereafter labeled as study 2, consists of additional 12 subjects (9 men, 3 women) with type 1 diabetes extracted from a larger dataset (unpublished data). Mean ± SD demographic information is age, 39.7 ± 9.8 years; duration of type 1 diabetes, 19.8 ± 9.1 years; HbA_{1c}, 56.8 ± 4.5 mmol/mol; and BMI, 24.4 ± 0.6 kg/m^2. The protocol of study 2 was originally designed to assess closed-loop control algorithms, but data from the control open-loop experiments are consistent with the aims of the present report and can thus be used to strengthen the results. Inclusion criteria were identical to study 1. Each participant wore one Dexcom SEVEN Plus CGM sensor, which was calibrated according to the manufacturer's instructions. At ~1600 h of the third day of monitoring, participants were admitted to the CRC and underwent randomly 24 h of open-loop treatment or closed-loop control. During admission, blood samples were collected for glucose measurements, usually every 30 min, every 15 min for 2 h after a meal, and every hour during nighttime. CGM and BG data of the 24 hospitalized hours during the open-loop portion of the experimental protocol were used for the present report.

Both protocols were approved the by local institution review boards of the participating centers listed above and all participants signed an informed consent form.

The sCGM sensor architecture

The block scheme in Fig. 1 shows the proposed architecture of the sCGM sensor. The data stream glucose values given in output by the commercial CGM sensor drives the cascade of three software modules, each dedicated to cope with one of the three issues—uncertainty, accuracy, and necessity of prediction—presented in the literature. All modules can work in real-time and in cascade to any CGM sensor, irrespective of the manufacturer. A notable feature of the three modules is their mutual independence (i.e., if one module is removed the others can still work). The order of the modules is fixed in such a way that the global utility will be maximized. In fact, before dealing with accuracy, it is beneficial to improve the signal-to-noise ratio. Similarly, prediction of future glucose levels is more reliable if CGM data are first smoothed and enhanced.

The architecture of the sCGM sensor of Fig. 1 allows for plug-in of any literature algorithm but, for illustrative purpose, the chosen algorithms in this report are denoising (17), enhancement (25), and prediction (26) methods recently proposed by our research group. Given the scope of *Diabetes Care,* we refer the interested reader to our earlier studies (17,25,26) for the technical details on the three algorithms. An only brief overview is given in the following section.

The sCGM sensor algorithms

The denoising module presented in Facchinetti et al. (17) is a digital filter that reduces the uncertainty due to measurement noise on CGM data. The filter receives in input the glucose value measured by the CGM sensor, performs in real time an estimation of variance of the measurement noise component, and returns in output a new, denoised, CGM value. The main feature of the filter is that it is self-tuneable, meaning that all algorithm parameters are automatically estimated for each individual without the need of user intervention and is adaptive (i.e., the denoising algorithm is able to cope with the intraindividual variability of the measurement noise). From a clinical perspective, the use of the denoising module can significantly reduce spurious oscillations and spikes on the CGM output that can generate false hypo- or hyperglycemic alerts, reducing the nuisance for the patient and increasing his or her confidence in the CGM device.

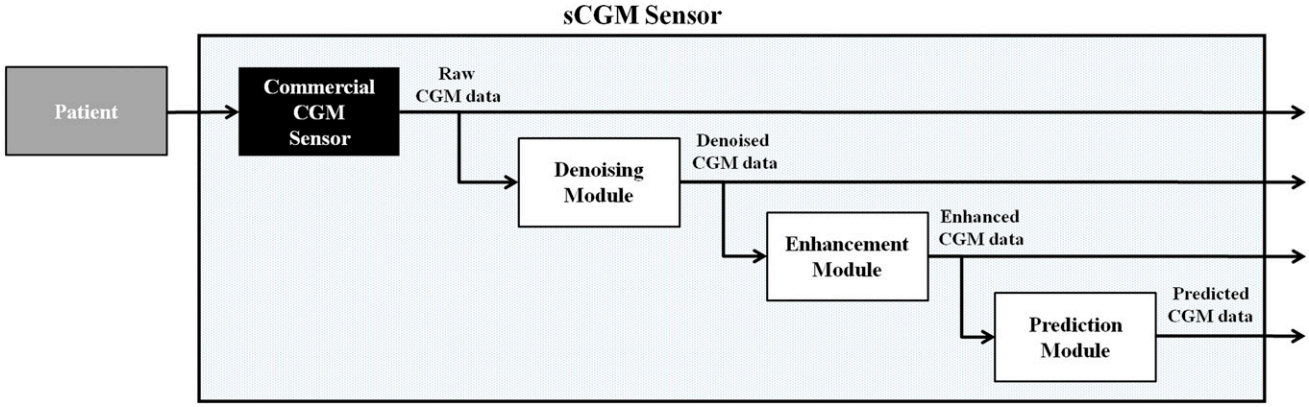

Figure 1—*The sCGM sensor architecture comprises a commercial CGM sensor (black block) and three software modules for denoising, enhancement, and prediction applied in cascade and working in real time. The denoising module receives in input CGM data and returns in output a smoother CGM profile. The enhancement module receives in input the smoothed CGM data and returns in output more accurate CGM data. Finally, the prediction module receives in input denoised and enhanced CGM data and returns in output the prediction of future glucose value, on which "preventive" hypo- and hyperglycemic alerts can be generated.*

The enhancement module presented by Guerra et al. (25) improves the accuracy of CGM by reducing systematic differences between reference BG measurements and CGM data due to, for example, BG-to-interstitial glucose kinetics and/or sensor drift. The method used within this module exploits the CGM data stream and the self-monitored BG (SMBG) data normally drawn by diabetic patients. When two suitable SMBG values are available, a portion of CGM data in correspondence to them is selected and a nonparametric deconvolution procedure is applied to estimate the BG values that should have generated that portion of CGM data. Then, the parameters of a linear regressor are estimated on that portion of data and applied in real time to subsequent CGM values to correct them and reduce systematic deviations from BG data not explained by BG-to-interstitial glucose kinetics. From a clinical perspective, the reduction of the amplitude of under- and overestimations of the CGM output with respect to BG references creates a more reliable CGM device: most of the undetected hypo- and hyperglycemic events can be recovered, increasing the usefulness of real-time monitoring and allowing patients to be more confident about the glucose value reported by the sensor, especially if it is used as tool to visualize their glycemia. An AP system will clearly benefit from the increased accuracy because the possibility of calculating a suboptimal insulin dose will be minimized.

The prediction module mitigates the occurrence of hypo- and hyperglycemic events by generating alarms when the short-term prediction of future glucose value exceeds hypo- and hyperglycemic thresholds. The predicted algorithm used here is the simple first-order autoregressive model pioneered by Sparacino et al. (26). Although more sophisticated prediction methods have been proposed in the literature, this simple method is well suited to the conceptual aim of the present report and has the advantage of having only one parameter, the forgetting factor μ (here $\mu = 0.925$ determined by minimizing the index J defined in Facchinetti et al. [34]). From a clinical perspective, the generation of a preventive hypo- or hyperglycemic alert allows the patient to be aware of the forthcoming critical event and take preventive measures (e.g., sugar intake in case of hypoglycemia) to avoid or mitigate its duration.

Outcome metrics

To quantify the improvement in the smoothness of the CGM time series thanks to the denoising module, we resorted to the energy of the second order differences (ESOD) of the CGM time series, a quantity widely used in the smoothing and regularization signal-processing literature to evaluate the smoothness of a profile (26,34). The greater the ESOD value, the more irregular the CGM time series and the more difficult its practical use (e.g., for hypoglycemic alert generation), given its uncertainty.

The accuracy of CGM data with respect to reference BG measurements has been quantified using the mean absolute relative difference (MARD) and the Clarke error grid (CEG). MARD is an index that assesses the point-to-point error of the CGM data and is widely used in literature (35). The CEG is a method that classifies each pair of CGM and BG values into five zones based on the clinical risk associated with possible discrepancies between CGM and BG. These zones are labeled from A to E, which signifies an increasing degree of harmfulness to the patient (36). CEG analysis is widely used to assess the output of CGM devices in a clinical context. As suggested by Clarke and Kovatchev (36), because almost all current CGM sensors achieve a performance of 98% of pairs classified in zones A+B, the percentage of pairs in zone A and the percentage in zone B should be reported separately.

Finally, concerning the prediction module, the ability of the prediction algorithm to generate preventive hypo- and hyperglycemic alerts has been evaluated by time gain in the detection of the event (i.e., how many minutes before the actual crossing is the algorithm able to predict a threshold crossing), and the number of false alerts (i.e., threshold crossing predicted by the algorithm, followed by no occurrence of the event).

RESULTS—In study 1, datasets of 11 of 12 patients were used because the CGM sensor 2 malfunctioned on day 2 of monitoring in subject 3. No datasets from study 2 were discarded.

An example of denoising is displayed in Fig. 2*A* (to allow readability, only the time interval 1200–2200 h of day 2 is shown). The improvement in smoothness and reduction of spurious oscillations,

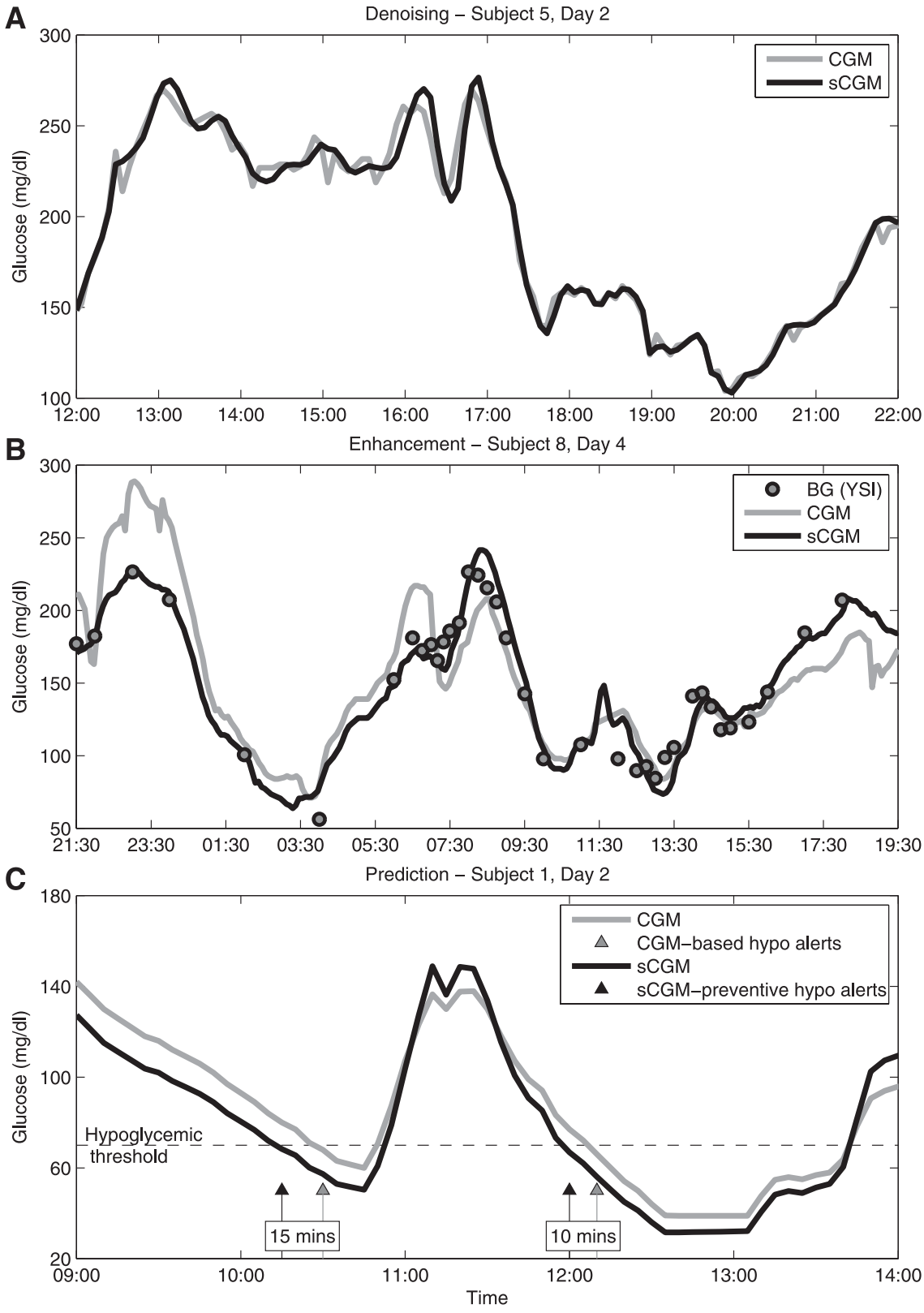

Figure 2—*Examples of the application of three modules for the sCGM sensor in three representative subjects.* A: *The denoised output of the sCGM sensor (black line) is compared with raw CGM data (gray line).* B: *The enhanced output of the sCGM sensor (black line) and raw CGM data (gray line) is compared with reference BG values (gray circles).* C: *The real-time prediction (black line) obtained from the sCGM output (gray line), the alerts generated by crossing the hypoglycemic threshold (black and gray arrows, respectively) and the temporal gain in forecasting these events thanks to prediction are shown. Note that the time scales on the x-axis of the three panels are different.*

evident by visual inspection (e.g., ~1230 and 1515 h), is quantified by a reduction of the ESOD value from 3.8 (original profile) to 1.9 (denoised profile). From a clinical perspective, this result is useful for avoiding, or at least limiting, spurious hypo- and hyperglycemic threshold crossings that could result in false alerts. For instance, on the total number of hypoglycemic events detected by CGM data in study 1+2, we quantified by visual inspection that ~7% of the alerts generated by simple threshold crossings are false alerts due to noise. With the denoising algorithm, this number is reduced to ~3%. Table 1 reports ESOD values, calculated on all 7 days of monitoring, of original and denoised CGM profiles for the 11 subjects of study 1, and those calculated on the 24 h of hospitalized monitoring from study 2. The reduction of the irregularity of CGM time series is significant, with the mean ESOD value lowered by ~45% (from 2.0 to 1.1, $P = 0.05$) for study 1, 71% (from 1.7 to 0.5, $P = 0.01$) for study 2, and 57% (from 1.8 to 0.8, $P < 0.01$) if study 1 and 2 are considered together. Of note, the delay introduced by the denoising module averages 2.1 ± 1.1 min, which is acceptable compared with the time sampling of the CGM sensor (5 min) and is in line with results presented in studies on other sensors (19).

Concerning the enhancement step, Fig. 2*B* depicts a comparison between CGM and sCGM sensor, which benefits from the algorithms of Guerra et al. (25), for subject 8 during the in-hospital study from 2130 h of day 3 to 1930 h of day 4, in which reference BG values were measured in parallel using YSI. Enhancement was performed by using two SMBG samples collected at 1950 and 2110 h of day 3 (data not shown for picture clarity). The improvement in accuracy of sCGM over the CGM sensor can be appreciated during the nighttime (from 2300 to 0600 h) and during breakfast, where the CGM profile is almost superimposed on the reference YSI values. The improvement in accuracy is also confirmed by a reduction in MARD from 11.6 to 6.6% and an increase in the pairs falling in zone A of the CEG from 87.5 to 96.6%, with 100% of pairs classified in zones A+B. From a clinical perspective, the improvement of

Table 1—*Results summary of the application of denoising and enhancement algorithms*

		Denoising		Enhancement							
						CEG (%)					
		ESOD		MARD (%)		CGM			sCGM		
	Patient	CGM	sCGM	CGM	sCGM	A	B	A+B	A	B	A+B
Study 1	1	4.1	2.1	30.6	6.8	29.4	67.6	97.1	100.0	0.0	100.0
	2	1.9	0.8	11.3	16.8	88.9	11.1	100.0	67.9	32.1	100.0
	3	1.1	1.0	13.1	7.3	83.3	16.7	100.0	100.0	0.0	100.0
	4	2.1	1.1	12.7	20.7	88.6	8.6	97.1	62.9	34.3	97.1
	5	3.8	1.9	25.2	9.6	42.1	55.3	97.4	84.6	15.4	100.0
	6	1.0	0.5	15.3	14.8	80.0	14.3	94.3	88.9	8.3	97.2
	7	1.6	0.8	13.4	11.2	69.2	30.8	100.0	79.5	20.5	100.0
	8	2.6	2.2	11.6	6.6	87.5	9.4	96.9	96.6	3.4	100.0
	9	1.4	1.1	15.2	11.0	66.7	33.3	100.0	86.1	11.1	97.2
	10	0.6	0.2	10.1	3.9	100.0	0.0	100.0	100.0	0.0	100.0
	11	1.3	0.6	13.3	10.7	73.5	26.5	100.0	87.5	12.5	100.0
	Mean	2.0	1.1*	15.6	10.9†	73.6	24.9	98.4	86.7	12.5	99.2
	SD	1.1	0.7	6.4	4.9	21.2	20.9	2.0	12.7	12.3	1.3
Study 2	1	0.2	0.1	11.2	10.2	75.6	24.4	100.0	85.4	14.6	100.0
	2	0.5	0.1	12.6	8.9	93.3	6.7	100.0	93.3	6.7	100.0
	3	1.6	0.6	26.8	13.7	44.4	55.6	100.0	85.2	14.8	100.0
	4	1.0	0.3	16.6	7.3	69.0	31.0	100.0	96.6	3.4	100.0
	5	3.6	1.4	7.6	5.2	90.0	10.0	100.0	93.3	6.7	100.0
	6	2.9	0.8	23.6	13.5	53.1	46.9	100.0	75.0	25.0	100.0
	7	1.4	0.5	15.7	11.0	65.4	15.4	80.8	84.6	7.7	92.3
	8	1.1	0.3	11.6	8.0	89.4	10.6	100.0	95.7	4.3	100.0
	9	5.7	1.3	25.3	20.9	54.5	45.5	100.0	56.8	43.2	100.0
	10	0.8	0.2	11.5	5.9	86.8	13.2	100.0	100.0	0.0	100.0
	11	1.5	0.4	7.4	4.8	95.5	4.5	100.0	100.0	0.0	100.0
	12	0.6	0.2	6.5	5.3	100.0	0.0	100.0	97.7	2.3	100.0
	Mean	1.7	0.5*	14.7	9.8†	76.4	22.0	98.4	88.6	10.7	99.4
	SD	1.6	0.5	7.1	4.9	18.8	18.6	5.6	12.6	12.5	2.2
Study 1+2	Mean	1.8	0.8*	15.1	10.3†	75.1	23.4	98.4	87.7‡	11.6§	99.3
	SD	1.4	0.6	6.6	4.8	19.6	19.3	4.1	12.4	12.2	1.8

*The mean irregularity value of sCGM was significantly lower than the original CGM ($P = 0.05$ in study 1, $P = 0.01$ in study 2, $P < 0.01$ in study 1+2). †The mean MARD value of sCGM was significantly lower than original CGM ($P = 0.04$ in study 1, $P = 0.05$ in study 2, $P < 0.01$ in study 1+2). ‡The mean percentage of couples of values of sCGM classified in the A zone of the CEG was significantly greater than original CGM ($P = 0.02$ in study 1+2). §The mean percentage of couples of values of sCGM classified in the B zone of the CEG was significantly lower than original CGM ($P = 0.02$ in study 1+2).

accuracy by the enhancement module can lead to important benefits in patient safety. In fact, if we focus at time 0400 h, we can observe that a hypoglycemic event was measured by YSI, but not by the CGM sensor (whose values remained over the 70 mg/dL threshold for the entire night without generating an alert). The sCGM sensor, however, would have generated an alert at ~0320 h, allowing the subject to take appropriate countermeasures to mitigate the hypoglycemic event.

Table 1 presents MARD values and CEG results for the 23 subjects. With the enhancement module, the mean MARD value has been significantly decreased from 15.6 to 10.9% ($P = 0.04$) in study 1, from 14.7 to 9.8% ($P = 0.05$) in study 2, and from 15.1 to 10.3% in study 1+2 ($P < 0.01$). By turning to CEG, on average, the Dexcom SEVEN Plus sensors used in this study performed satisfactorily (98.4% of data pairs classified in zones A+B). However, the percentage of points classified in zone B was still elevated (>23%). With the enhancement module, we achieved a significant increase in the number of CGM values classified as accurate (zone A), from 75.1% of original to 87.7% ($P = 0.02$). We can highlight some other important aspects in the improvement in accuracy:

First, the performance of the original CGM Dexcom SEVEN Plus sensor is in line with that reported by Kovatchev et al. (35) and Garg et al. (37), with an overall MARD value ~15 to 16% and percentage of CGM values classified in zones A+B from ~98 to 99%.

Second, if we consider the results (i.e., MARD, 0.3%; percentage in zone A, 87.7%; and percentage in zones A+B, 99.3%), the sCGM sensor seems to outperform all of the most recent commercial CGM devices. For instance, the recently launched Enlite sensor (Medtronic Diabetes, Northridge, CA) achieves an overall MARD of ~13.8% and percentage in zone A of 78.4% (38). Obviously, this is a largely speculative comparison because results were derived from two different datasets.

Finally, an example of how the prediction module works is displayed in Fig. 2*C*, where representative data of subject 1 are shown (again, to improve readability of the picture, a limited time interval, 0900–1400 h of day 2, is considered). Two hypoglycemic alerts are generated by comparing the 70-mg/dL threshold with the sCGM profile at times 1030 and 1210 h, respectively, and the prediction module allows generating preventive hypoglycemic alerts at times 1015 and 1200 h, respectively. This means that the patient can be warned of the occurrence of these two critical events 15 and 10 min ahead of time, respectively. This can be extremely useful from a clinical perspective, because it allows the patient to act timely to avoid, or at least mitigate, critical events by taking an appropriate countermeasure (e.g., carbohydrate intake in case of imminent hypoglycemia). Table 2 presents the results of the application of the prediction module to the whole dataset. For hypoglycemia, 95 episodes in study 1+2 were detected by sCGM data. The prediction algorithm was able to forecast all these events with an average amount of 13 min gained before the hypoglycemic threshold crossing of the sCGM trace. Focusing on hyperglycemia, 141 episodes in study 1+2 were detected by sCGM, which were predicted an average of 15 min ahead of time.

Also of particular practical interest is the evaluation of the number of false hypo- and hyperglycemic alerts when prediction profiles are exploited. This is a well-known problem in the literature, because measurement noise that unavoidably affects the CGM output is amplified when performing glucose prediction (12). To better assess the usefulness of the sCGM sensor architecture, for study 1 we applied the prediction module on the original CGM data (i.e., without the preprocessing performed by the denoising module) and obtained a percentage of false alerts of ~42%. Conversely, if prediction is computed after denoising, the percentage of false alerts is reduced to 20%. This demonstrates that the number of preventive false alerts can be more than halved if sCGM output is used.

Table 2—*Results summary of the application of the prediction module*

		Prediction			
		Hypoglycemic events		Hyperglycemic events	
	Patient	*N*	Time gain min	*N*	Time gain min
Study 1	1	11	16	9	12
	2	4	10	13	6
	3	3	17	9	14
	4	6	8	14	20
	5	5	8	13	15
	6	6	19	10	16
	7	1	5	18	16
	8	11	18	12	14
	9	6	10	7	19
	10	4	14	8	20
	11	3	15	10	13
	Global*	60	14	123	15
Study 2	1	3	11	1	11
	2	3	14	N/A	N/A
	3	6	11	2	13
	4	5	11	2	17
	5	3	8	2	14
	6	3	19	2	11
	7	6	11	N/A	N/A
	8	N/A	N/A	N/A	N/A
	9	5	14	1	10
	10	1	30	2	14
	11	N/A	N/A	3	15
	12	N/A	N/A	3	13
	Global*	35	12	18	13
Study 1+2	Global*	95	13	141	15

N/A, events not observed for that patient. *For the number of events, "global" means the total number of events, whereas for time gain, "global" is the average among subjects (weighted for the number of events occurred per subject).

CONCLUSIONS—CGM systems are currently used by diabetic patients mainly for real-time monitoring of their glucose values and for generation of hypo- and hyperglycemic alerts. They are also a key component of sensor-augmented insulin pumps and closed-loop systems. However, their performance is still suboptimal, and margins of improvement are present for uncertainty, accuracy, and delay in the detection of hypo- and hyperglycemic events.

In this report we presented the concept of the sCGM, which is composed of a commercial CGM system to which three software modules working in real time are placed in cascade to the sensor. By using the denoising module, a reduction in the "irregularity" of CGM profiles by 45% could be achieved, adding only a minimal delay to the CGM readings. In practice, limiting the irregularity of CGM data can be extremely useful to reduce the number of false hypo- and hyperglycemic alerts generated by the CGM system, with obvious benefits for the diabetic patient.

The enhancement module significantly reduces point-to-point differences between reference BG and glucose sensor values, improving CGM accuracy (determined using MARD) by more than 30%. In practice, this means an increase of the safety of the patient, especially during nighttime, when the patient is sleeping and an accurate continuous monitoring is needed to detect possible threatening hypoglycemic events.

Finally, the prediction module allows the sCGM sensor to forecast hypo- and hyperglycemic events an average of 15 min before they occur. In practice, prealerts will enable the patient to take prompt countermeasures to mitigate, or even avoid, hypo- and hyperglycemic events (e.g., sugar intake or insulin pump shut-off in case of forecasting of hypoglycemia).

The three modules of the sCGM (denoising, enhancement, and prediction) have been previously tested, as stand-alone applications, on two different types of CGMs, the FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA) and Glucoday (Menarini Diagnostics, Florence, Italy) (17,25,26). In the present report, we combined them in cascade for the first time and applied them to the SEVEN Plus CGM sensor data to show their added value and generalizability of use. The case studies considered in the present report show that denoising, enhancement, and prediction algorithms can indeed render commercial CGM systems more reliable and more efficient, and this can be of great benefit for several applications, especially AP implementations in which uncertainty and accuracy of CGM data strongly influence the effectiveness of control action. The next step in sCGM sensor development will be its real-time implementation within clinical trials that will be performed in the next 2 years by the AP@home project. Because, at the present time it is not possible to implement the sCGM sensor algorithms directly into the software used by the commercially available CGM systems, they will be placed between the output of the (commercial) CGM sensor and the data input of the closed-loop control algorithm (Fig. 1).

In conclusion, CGM accuracy is determined not only by the efficiency of the electrochemical process used but also by the way the stream of data is processed algorithmically. With an sCGM, the delay between BG and CGM-reported glucose can be overcome and hypoglycemia predicted with a time-horizon that allows the patient to take action before hypoglycemia occurs.

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A.F. designed the algorithms and the study protocol, performed the analysis, wrote the manuscript, and contributed to the final draft of the manuscript. G.S. designed the algorithms, reviewed data analysis, contributed to results interpretation, edited the manuscript, and contributed to the final draft of the manuscript. S.G. designed the algorithms and the study protocol and contributed to performing the analysis and to the final draft of the manuscript. Y.M.L. and J.H.D.V. were responsible for clinical trials and data acquisition at the Academic Medical Center Amsterdam (Amsterdam, the Netherlands) and contributed to the final draft of the manuscript. J.K.M. and M.E. were responsible for clinical trials and data acquisition at the Medical University of Graz (Graz, Austria) and contributed to the final draft of the manuscript. C.B. and L.H. were responsible for clinical trials and data acquisition at the Profil Institute for Metabolic Research GmbH (Neuss, Germany) and contributed to the final draft of the manuscript. D.B. and A.A. were responsible for clinical trials and data acquisition at the Department of Clinical and Experimental Medicine, University of Padova (Padova, Italy) and contributed to the final draft of the manuscript. C.C. supervised the study and reviewed the manuscript. C.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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