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ORIGINAL ARTICLE

Retrofitting Real-Life Dexcom G5 Data

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Abstract

Background: We proposed in 2014 a retrofitting algorithm to retrospectively increase the accuracy of continuous glucose monitoring (CGM) data by using some blood glucose (BG) measurements. The method proved effective on Dexcom SEVEN Plus when about 10 highly accurate YSI measurements/session were available. In this study, we test the method on Dexcom G5 sensor in a more realistic setup, where only five capillary BG measurements (self-monitoring blood glucose [SMBG]) per 12 h-session are available. Furthermore, we investigate how accuracy is affected by the number of BG measurements.
Method: The algorithm was tested in 51 adults and 46 adolescents studied for 7 days with Dexcom G5. Each patient also underwent an $\sim$12-h hospital admission where frequent SMBG and YSI measurements were collected. First, five SMBGs per 12-h session were used to retrofit the CGM. Then, we varied the number of SMBGs provided to the method from 2 to 10 per 12-h session.
Result: Retrofitted CGM traces with five SMBGs per 12-h session have lower mean absolute difference than original CGM, reduced from 16.2 to 10.7 mg/dL ($P < 0.001$) in adults and from 17.6 to 11.5 mg/dL ($P < 0.001$) in adolescents, and mean absolute relative difference is reduced from 9.0% to 6.4% ($P < 0.001$) in adults and from 10.3% to 6.8% ($P < 0.001$) in adolescents. Reducing the number of BG measurements reduces improvement in the accuracy from >30% with 10 SMBGs per 12-h session to <16% with 2 SMBGs/day.
Conclusion: The retrofitting method retrospectively improves the accuracy of CGM data, even if applied to one of the most accurate CGM sensors currently available on the market.

Keywords: Continuous glucose monitoring, Sensor enhancement, Artificial pancreas, Retrospective sensor processing.

Introduction

Continuous Glucose Monitoring (CGM) technology has been constantly improving since its first appearance two decades ago, and CGM is now spreading in clinical practice.[1] CGM can be profitably used as an addition to self-monitoring blood glucose measurements (SMBGs) to improve glucose control by using the glucose trends in time measured by the device to adjust insulin dosing in real time.[2] Furthermore, the recorded CGM traces can be downloaded and used retrospectively for many purposes, for instance, for glucose pattern analysis and to adjust standard therapy parameters (e.g., basal pattern, carbohydrate-to-insulin ratio),[3] to assess glucose control achieved in a clinical trial,[4] to estimate physiological model parameters,[5] and to identify glucose–insulin models.[6,7]

Recently, we proposed a retrofitting algorithm,[8] that is, a retrospective technique designed to improve a posteriori the accuracy of a CGM trace by using a few SMBGs collected in parallel with the CGM. By merging information of CGM (high-temporal resolution) and SMBGs (sparse in time, but more accurate than CGM), the retrofitting method produces a continuous-time blood glucose (BG) profile, which is more accurate than the original CGM data. Having a more accurate CGM trace is beneficial for the abovementioned applications. In particular, in a previous article,[9] we showed that retrofitting Dexcom SEVEN Plus traces allows better estimation of glucose control metrics such as the mean glucose, percent of time spent in hypoglycemia, and percent of time spent with glucose in target range (70–180 mg/dL). Furthermore, in Ref.,[9] we showed that the retrofitting algorithm is more effective than other simpler techniques. The main limitation of the analysis proposed in Ref.[9] was related to the testing setup: although realistic, it was admittedly favorable to the retrofitting method. In fact, a relatively large number of highly accurate references (YSI) were provided to the retrofitting

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method to retrospectively process the Dexcom SEVEN Plus data. It remained to be proven that the retrofitting method could still be beneficial in other more challenging setups, characterized by the availability of less and less accurate references, such as SMBG. Furthermore, it was unclear if the increased accuracy of the new generation of Dexcom sensor could be further improved by the retrofitting method.

The first objective of this article is to investigate these issues, in particular if the retrofitting method is still effective when (1) the method is applied to Dexcom G5, a new-generation sensor that reached one-digit precision and that is currently one of the most accurate CGM sensors on the market; and (2) only five SMBGs are collected by the patient in a 12-h session. In fact, it can be expected that five SMBGs are collected in a 12-h diurnal session when a CGM sensor is used adjunctively to SMBG: for example, two SMBGs for calibration (one at the beginning and one at the end of the session), plus three SMBG checks related to the meals.

The second objective of the article is to investigate how the accuracy improvement granted by the retrofitting method is affected by the number of BG measurements available. In fact, our method leverages on these BG measurements to improve CGM and as a consequence, accuracy degradation should be expected as few of them become available. In this work, we analyze both the cases when more or less than five SMBGs are collected during the 12-h session: more than five SMBGs are expected to be collected by a compliant patient, verifying the CGM reading with an SMBG before taking any therapeutic decision, that is, at each meal, 2 h after each meal, and in case of hypo or hypoglycemia requiring interventions; less than five SMBGs are likely collected by a noncompliant patient or in a 12-h portion, including the night. Furthermore, only two SMBGs per day (calibrations) are available in case of nonadjunctive use of CGM, a possible future scenario given the recent U.S. Food and Drug Administration panel meeting where the panel expressed a positive opinion about the change of the label of Dexcom G5 sensor from adjunctive to nonadjunctive.[10]

The investigation presented here is conducted on both adults and adolescents.

Methods

Data

Original dataset. The retrofitting algorithm was tested on the data collected in 51 adult subjects, reported in Ref.,[11] and in 46 adolescents, 13–17 years old, presented in Ref.[12] Both groups of subjects wore the Dexcom G5 for 7 days and had a 12-h in-clinic session on day 1, 4, or 7. During the admission, accurate BG references were collected with YSI instrument (Yellow Springs, OH) about every 15 min on arterialized venous samples and capillary SMBGs about every 30 min using the Bayer USB Contour Next meter.

Remark: We should point out that the data in both Refs.[11,12] were actually collected using the Dexcom G4 equipped with the software 505 (also known as G4AP) and not with the Dexcom G5. Nevertheless, the two models can be considered, for the purpose of this article, completely equivalent. Sensing and signal processing technologies are instead identical and the only difference in the two products is in the data transmission hardware: G4 with software 505 requires an ad hoc receiver, while G5 allows direct data transmission and processing on the patient's smartphone.

Real-life-like datasets. To mimic a real-life outpatient setting, only a small fraction of the available SMBGs were provided to the retrofitting algorithm to enhance the accuracy of a CGM trace. At first, we provided to the method $N_{SMBG} = 5$ references per 12-h session since five SMBGs are likely to be collected during the daytime when the CGM sensor is used adjunctively to SMBGs. Uniform SMBGs, subsampling was used, retaining one SMGB every X available ones, with X suitably chosen to get the desired total number N_{SMBG}.

Then, to study the impact of the number of available SMBGs on the accuracy achieved by the retrofitting method, we let the number of SMBGs provided to the method vary from $N_{SMBG} = 10$ to $N_{SMBG} = 2$ per 12-h session, spanning both the cases when more or less than $N_{SMBG} = 5$ are available. For the case, $N_{SMBG} = 2$ per 12-h session, two calibration SMBGs were used.

Figure 1 (upper panel) illustrates the real-life-like dataset for $N_{SMBG} = 5$.

The retrofitting algorithm

The retrofitting method that we proposed in Ref.[8] is a retrospective technique designed to improve a posteriori the accuracy of a CGM trace using a few SMBGs collected in parallel with CGM. The method merges the complementary information contained in these two sources, the high-temporal resolution of CGM and better (vs. CGM) accuracy brought by the SMBGs, to produce a continuous-time BG profile, which is more accurate than the original CGM data.

Figure 1 (central panel) illustrates the inputs of the retrofitting algorithm, that is, CGM (dashed line) and the few SMBGs (solid dots) in a representative adult patient. The panel also shows the output of the method, the retrofitted CGM (solid thick line).

Accuracy improvement can be clearly seen by comparing original CGM and retrofitted CGM with the YSI references available (diamonds). We remark that YSI references were not used in the retrofitting algorithm.

Figure 1 (lower panel) illustrates the case in which only two calibration SMBGs are available, $N_{SMBG} = 2$ SMBGs per 12-h session. Thanks to the retrospective information carried by the calibration SBMGs, and in particular to the a posteriori correction based on the last SMBG, the method is still able to improve the accuracy of the CGM signal, although the improvement is smaller than when $N_{SMBG} = 5$ per 12-h session are available.

A succinct description of the method can be found in the Appendix of this article, whereas a detailed presentation of all the mathematical details can be found in Ref.[8]

Accuracy outcome metrics

Original CGM and retrofitted CGM values are matched with the YSI measurements performed at the same time.

The main metrics used to assess the accuracy of signals are the absolute difference (AD) and the absolute relative difference (ARD).These metrics are computed for each data pair. Then, the overall mean (standard deviation) is reported for normally distributed metrics and

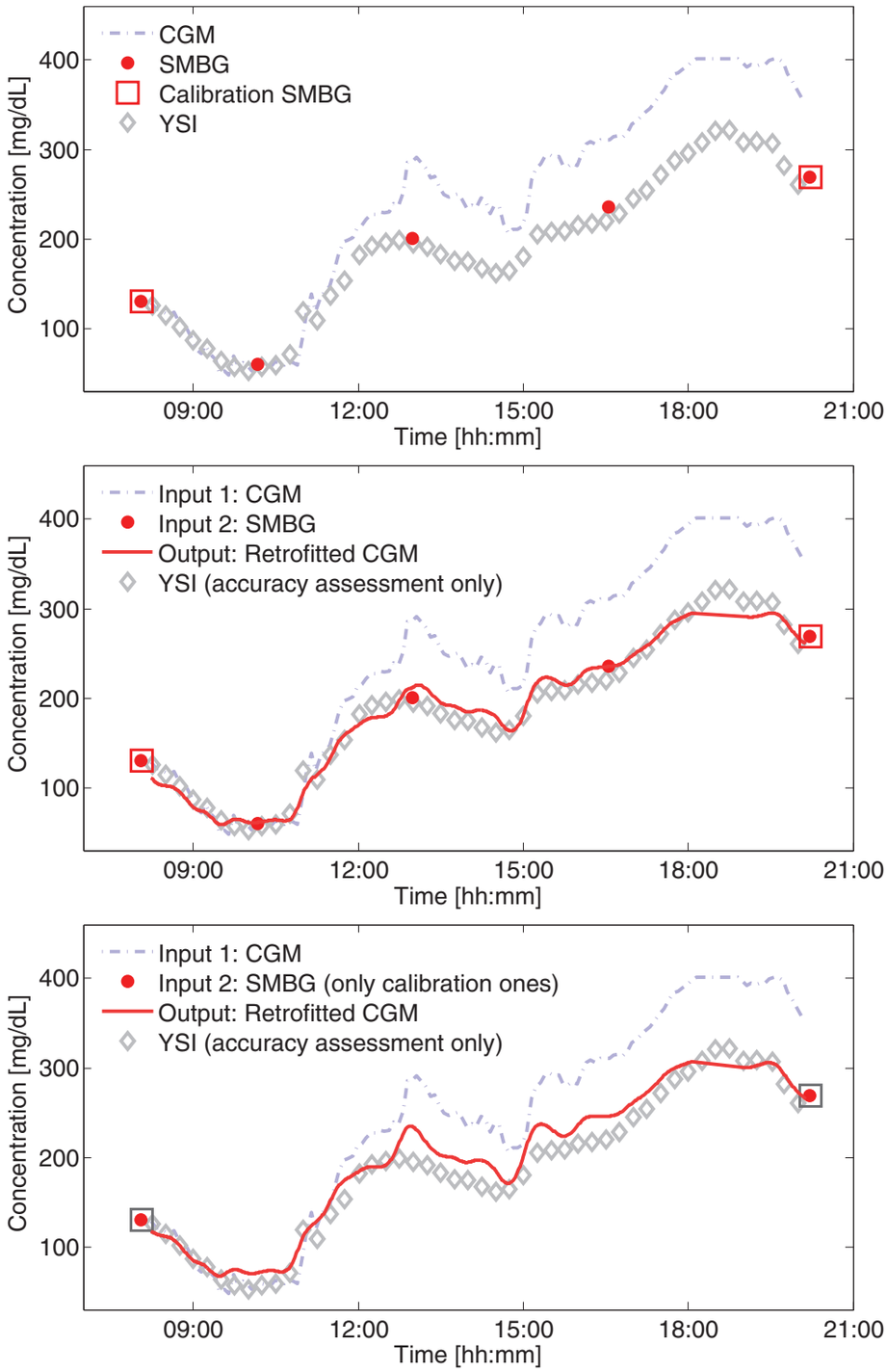

FIG. 1. Upper panel: Example of a representative dataset (adult patient). The dashed trace represents the CGM readings, solid dots denote the SMBGs used to retrofit. Of the many SMBGs available in the dataset, only $N_{SMBG}=5$ SMBGs per 12-h session have been retained to simulate an outpatient study. SMBGs previously used for CGM calibration are highlighted by the square. The diamonds are the YSI references used to test the accuracy of both CGM and retrofitted CGM. Central panel: Inputs (CGM and reference BG) and outputs (red solid line) of the retrofitting algorithm. Note that YSI references are used exclusively to test the accuracy of both CGM and retrofitted CGM and not to produce the retrofitted profile. The accuracy improvement brought by the method is clearly visible. Lower panel: Retrofitting CGM exploiting only two calibration SMBGs ($N_{SMBG}=2$ SMBGs per 12-h session). BG, blood glucose; CGM, continuous glucose monitoring; SMBG, self-monitoring blood glucose.

population median [25th–75th] percentile is reported for non-normally distributed metrics. Normality is assessed with Lilliefors test.

We have also computed the percent of data matching the International Organization for Standardization (ISO) 15197:2013 15%/15%, that is, the percent of data falling within either 15 mg/dL from the YSI measurement if the YSI <100 mg/dL or within 15% of YSI if YSI >100 mg/dL. This metric is used to evaluate the acceptability of capillary home glucose monitoring meters.[13] We considered also other ranges, specifically the 5%/5%, 10%/10%, and 20%/20% ranges.

To evaluate interpatient variability of the accuracy, we computed for each patient mean AD (MAD), mean ARD (MARD), and the percent of point following the mentioned ISO ranges (ISO 5%/5%, ISO 10%/10%, ISO 15%/15%, and ISO 20%/20%). Then, the population mean (standard deviation) is reported for normally distributed metrics and population median [25th–75th] percentile is reported for non-normally distributed metrics.

To evaluate the accuracy in different glycemic regions, the above metrics are evaluated separately on points falling in the euglycemic range (70 mg/dL ≤ YSI ≤180 mg/dL), hypoglycemic range YSI ≤70 mg/dL, and hyperglycemic range YSI ≥180 mg/dL.

Finally, clinical accuracy is assessed with the Clark Error Grid analysis[14] by reporting the percentage of data points falling in zone A.

Statistics

Original and retrofitted CGM performance is compared with a paired *t*-test for normally distributed metrics and with a Wilcoxon signed-rank test for non-normally distributed data.

Results

Retrofitting G5 data

At first, we focus on the comparison between the original and retrofitted CGM data in the scenario in which $N_{SMBG} = 5$ measurements per 12-h session are used.[2] Table 1 reports, for both datasets, the accuracy metrics evaluated on all the available original CGM-YSI and retrofitted CGM-YSI data pairs.

By retrofitting, the mean of AD is significantly reduced in both populations: from 16.2 to 10.7 mg/dL ($P < 0.001$) in adults (about 34%) and from 18.1 to 11.9 mg/dL ($P < 0.001$) in adolescents (about 34%). Similarly, the mean of ARD was significantly reduced by about 29% and 34% in the two populations: from 9.0% to 6.4% ($P < 0.001$) in adults and from 10.7% to 7.1% ($P < 0.001$) in adolescents. The boxplots of AD and ARD distribution are reported in Figure 2 to further illustrate these findings. The improved accuracy is confirmed also by the increased number of points matching the ISO criteria.

As detailed in Table 1, improvements in both AD and ARD are confirmed in each glycemic region. Focusing, for instance, on ARD in adults, this metric was reduced from

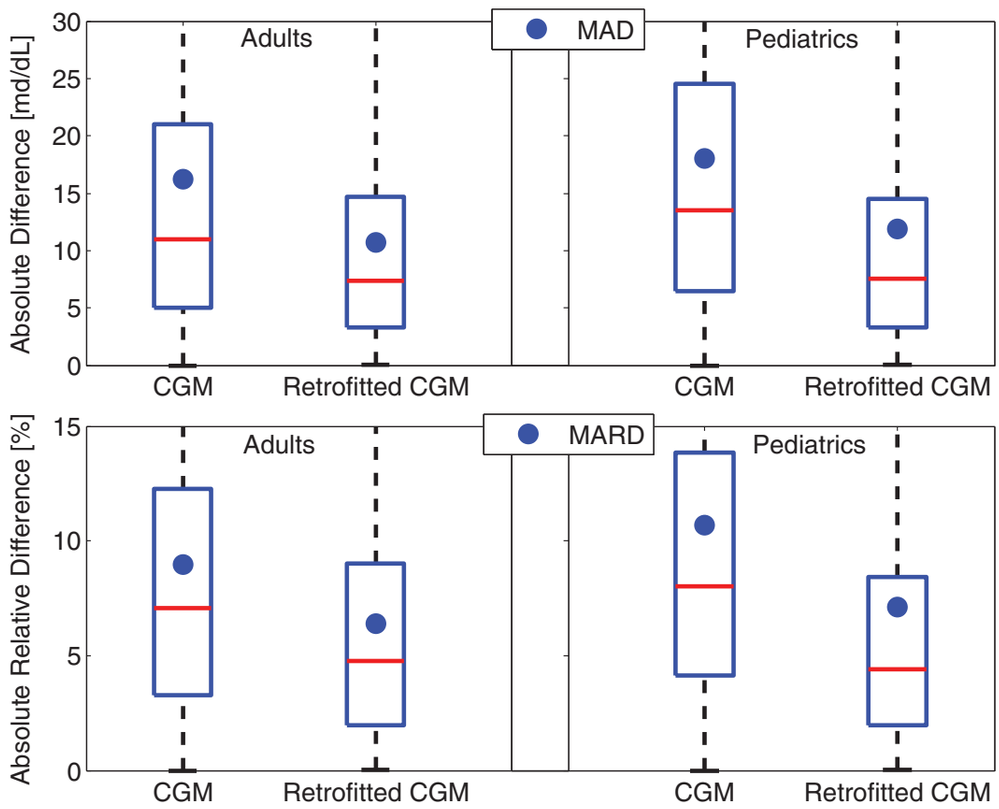

FIG. 2. Distributions of absolute difference and absolute relative difference of the original CGM and of the retrofitted CGM obtained with five SMBGs per 12-h session. The improvement granted by the method is clearly visible.

Table 1. Accuracy Metrics Evaluated, for Both Datasets, on All the Available Original CGM-YSI and Retrofitted CGM-YSI Data Pairs

	Adults			*Pediatrics*		
Metric, units	*CGM*	*Retrofitted CGM*	P	*CGM*	*Retrofitted CGM*	P
Overall						
Number of paired data, #	2241	2263		1913	1918	
AD, mg/dL	16.2 (17.0)	10.7 (10.6)	**<0.001**	18.1 (18.1)	11.9 (16.6)	**<0.001**
ARD, %	9.0 (7.9)	6.4 (6.0)	**<0.001**	10.7 (10.9)	7.1 (9.5)	**<0.001**
Percent point ISO, %						
5%/5%	39.3	54.6	—	32.2	56.6	—
10%/10%	69.2	82.7	—	63.6	82.8	—
15%/15%	85.9	93.5	—	81.2	91.2	—
20%/20%	92.9	97.6	—	90	95.5	—
CEG—zone A, %	92.5	97.1	—	88.6	94.6	—
Hypoglycemia						
Number of paired data, #	255	260		130	134	
AD, mg/dL	6.4 (5.2)	5.1 (4.0)	**0.008**	10.5 (8.2)	8.1 (8.9)	**0.003**
ARD, %	11.0 (9.6)	8.8 (7.1)	**0.009**	17.4 (15.1)	13.6 (15.7)	**0.003**
Percent point ISO, %						
5%/5%	45.9	53.5	—	23.8	43.3	—
10%/10%	75.3	89.6	—	54.6	72.4	—
15%/15%	91.4	97.7	—	77.7	88.8	—
20%/20%	97.3	98.8	—	89.2	92.5	—
CEG—zone A, %	95.3	98.1	—	83.8	85.8	—
Euglycemia						
Number of paired data, #	834	841		779	777	
AD, mg/dL	11.3 (10.1)	9.1 (8.3)	**<0.001**	14.6 (14.9)	9.2 (11.8)	**<0.001**
ARD, %	9.6 (7.9)	7.8 (7.0)	**<0.001**	12.2 (11.9)	7.9 (10.1)	**<0.001**
Percent point ISO, %						
5%/5%	33	45.3	—	28.8	51.5	—
10%/10%	63.1	73.6	—	57.1	78.2	—
15%/15%	83.7	88.2	—	73.6	88.8	—
20%/20%	92	95	—	83.7	94.5	—
CEG—zone A, %	91.1	93.9	—	81.1	93.3	—
Hyperglycemia						
Number of paired data, #	1152	1162		1004	1007	
AD, mg/dL	21.9 (20.4)	13.1 (12.3)	**<0.001**	21.7 (20.4)	14.6 (19.7)	**<0.001**
ARD, %	8.0 (7.2)	4.9 (4.4)	**<0.001**	8.7 (8.6)	5.6 (7.2)	**<0.001**
Percent point ISO, %						
5%/5%	42.4	61.5	—	36	62.4	—
10%/10%	72.2	87.8	—	69.7	87.8	—
15%/15%	86.4	96.5	—	87.6	93.4	—
20%/20%	92.6	99.1	—	95	96.7	—
CEG—zone A, %	92.8	99.1	—	95	96.7	—

The retrofitted CGM was obtained with 5 SMBGs per 12-h session. Boldface highlights P values smaller than $P < 0.05$.

CEG, Clark Error Grid analysis; CGM, continuous glucose monitoring; ISO, International Organization for Standardization; SMBG, self-monitoring blood glucose.

11.0% to 8.8% in hypo ($P < 0.01$) and from 9.6% to 7.6% in euglycemia ($P < 0.001$), while the improvement is even more evident in hyperglycemia, passing from 21.9% to 13.1% ($P < 0.001$); in adolescents, ARD improved from 17.4% to 13.6% ($P = 0.003$) in hypoglycemia, from 12.2% to 7.9% ($P < 0.001$) in euglycemia, and from 8.7% to 5.6% in hyperglycemia.

Table 2 reports the patient-level analysis. All metrics are computed for each patient, and then the distribution among 51 adults and 46 adolescents is considered. Overall, MAD and MARD are significantly reduced in both populations by retrofitting. In adults, mean MAD is reduced by 34%, from 16.5 to 10.8 mg/dL, $P < 0.001$, and mean MARD by 28%, from 9% to 6.7%, $P < 0.001$. Similarly, in adolescents, mean MAD is reduced by 37%, from 19.1 to 12.1 mg/dL, and mean MARD by 36%, from 11.3% to 7.2%. The improved accuracy is also confirmed by the significant increase in the percent of points matching the ISO criteria.

For what concerns the patient-level analysis in each glycemic region (Table 2), MAD and MARD improvements are statistically significant in all the regions for adolescents. Mean MAD and mean MARD reduction goes from 28% to 35%. In adult patients, instead, a significant improvement of about 15% in both metrics is detected in euglycemia and a highly significant improvement of 40% is detected in hyperglycemia, while in the hypoglycemic range, only a trend toward roughly 25% improvement is found ($P = 0.062$ for MAD and $P = 0.077$ for MARD).

Table 2. Patient-Level Analysis: The Metrics Are Computed for Each Patient and Then the Distribution Among 51 Adults and 46 Adolescents Is Reported

	Adults			*Pediatrics*		
Metric, units	*CGM*	*Retrofitted CGM*	P	*CGM*	*Retrofitted CGM*	P
Overall						
Number of paired data, #	43.9 (6.8)	44.4 (7.4)		41.6 (8.5)	41.7 (8.3)	
MAD, mg/dL	16.5 (9.7)	10.8 (4.8)	**<0.001**	19.1 (13.8)	12.1 (10.6)	**<0.001**
MARD, %	9.0 (4.1)	6.4 (2.6)	**<0.001**	11.3 (7.3)	7.2 (5.4)	**<0.001**
Percent point ISO, %						
5%/5%	38.5 (18.9)	54.2 (20.8)	**<0.001**	30.7 (20.3)	56.3 (21.3)	**<0.001**
10%/10%	68.6 (22.0)	82.2 (16.0)	**<0.001**	61.2 (24.8)	82.5 (19.8)	**<0.001**
15%/15%	85.7 (16.9)	93.3 (9.3)	**0.001**	78.5 (24.3)	91.0 (15.3)	**<0.001**
20%/20%	92.8 (13.9)	97.5 (5.6)	**0.002**	88.0 (19.0)	95.2 (11.2)	**<0.001**
CEG—zone A, %	92.4 (13.8)	97.0 (5.9)	**0.002**	86.4 (19.6)	94.3 (11.3)	**<0.001**
Hypoglycemia						
Number of paired data, #	5.0 (4.0)	5.1 (4.0)		2.8 (2.4)	2.9 (2.4)	
MAD, mg/dL	7.2 (5.0)	5.4 (3.5)	0.062	12.1 (8.2)	8.6 (8.7)	**0.004**
MARD, %	12.1 (8.6)	9.3 (6.2)	0.077	19.9 (14.5)	14.2 (15.3)	**0.002**
Percent point ISO, %						
5%/5%	41.6 (39.1)	51.9 (38.4)	0.220	19.1 (25.3)	43.5 (37.6)	**0.011**
10%/10%	69.3 (38.6)	86.2 (24.2)	**0.034**	45.5 (39.7)	69.9 (38.6)	**0.009**
15%/15%	88.3 (25.9)	95.7 (13.2)	0.206	69.3 (38.6)	87.7 (28.3)	**0.008**
20%/20%	95.9 (16.0)	98.3 (8.3)	0.438	83.9 (32.0)	91.5 (26.6)	0.203
CEG—zone A, %	93.1 (19.4)	98.1 (6.7)	0.133	81.9 (32.0)	83.2 (31.9)	0.957
Euglycemia						
Number of paired data, #	16.4 (8.6)	16.5 (8.6)		16.9 (7.6)	16.9 (7.7)	
MAD, mg/dL	11.3 (5.7)	9.6 (4.6)	**0.012**	15.3 (10.9)	9.9 (7.7)	**<0.001**
MARD, %	9.6 (4.5)	8.1 (3.6)	**0.007**	12.8 (8.6)	8.6 (6.7)	**<0.001**
Percent point ISO, %						
5%/5%	35.0 (24.9)	41.8 (24.5)	0.122	29.4 (23.0)	48.4 (24.5)	**<0.001**
10%/10%	64.3 (23.6)	70.1 (25.1)	**0.041**	56.0 (27.9)	76.6 (25.3)	**<0.001**
15%/15%	82.8 (18.0)	86.7 (17.1)	0.061	73.2 (25.7)	87.2 (20.2)	**<0.001**
20%/20%	90.6 (15.1)	95.3 (9.6)	**0.015**	82.9 (21.5)	93.2 (15.2)	**<0.001**
CEG—zone A, %	89.9 (15.4)	94.3 (10.1)	**0.027**	80.5 (22.5)	91.9 (16.1)	**0.001**
Hyperglycemia						
Number of paired data, #	22.6 (7.1)	22.8 (7.6)		21.8 (9.8)	21.9 (9.8)	
MAD, mg/dL	22.5 (15.4)	13.3 (7.4)	**<0.001**	23.1 (18.0)	15.5 (20.2)	**<0.001**
MARD, %	8.4 (5.9)	5.0 (2.5)	**<0.001**	9.3 (7.3)	6.0 (7.0)	**<0.001**
Percent point ISO, %						
5%/5%	40.8 (29.4)	60.2 (27.4)	**<0.001**	34.4 (27.5)	61.6 (27.7)	**<0.001**
10%/10%	69.4 (32.4)	87.4 (17.6)	**<0.001**	66.9 (30.2)	87.1 (22.4)	**<0.001**
15%/15%	84.4 (24.5)	96.7 (7.1)	**0.001**	84.5 (26.0)	93.1 (19.1)	**<0.001**
20%/20%	91.8 (19.6)	99.1 (2.9)	**0.004**	93.3 (17.7)	95.9 (15.0)	0.151
CEG—zone A, %	92.3 (18.3)	99.1 (2.9)	**0.006**	93.3 (17.7)	95.9 (15.0)	0.151

The retrofitted CGM was obtained with 5 SMBGs per 12-h session.

Accuracy versus number of references

Figure 3 shows how the retrofitted CGM accuracy changes when the number of SMBGs varies. Upper panels report the mean absolute difference (mean AD) for the two populations, while the lower panels report the mean ARD.

When many SMBGs are available (8 to 10 in a 12-h session), the retrofitted trace is nearly as accurate as the SMBG: for $N_{SMBG} = 10$ references per 12-h session, MAD is reduced by about 38% in adults and by 45% in adolescents and similarly MARD is reduced by 30% and 45%, respectively. The benefit of retrofitting decreases gradually as the number of SMBGs decreases: for $N_{SMBG} = 5$ references per 12-h session, the improvements in both metrics are around 30%, as previously discussed; when only $N_{SMBG} = 2$ references per 12-h session are available, the reduction is lower, but still statistically significant: MAD decreases from 16.2 to 13.6 mg/dL ($P < 0.001$) in adults (about 16%) and from 18.1 to 15.7 mg/dL ($P < 0.001$) in adolescents (about 13%); similarly, MARD reduction is from 9.0% to 8.2% ($P < 0.001$) in adults (about 9%) and from 10.7% to 9.5% ($P < 0.001$) in adolescents (about 11%).

Discussion

The retrofitting method is a retrospective technique designed to improve a posteriori the accuracy of a CGM trace recorded by subjects with diabetes. The correction performed by the method relies on the information carried by some SMBGs, commonly collected by the patients. As such, the efficacy of the method strongly depends on the quality (e.g., YSI/Hemocue vs. SMBG) and on the number of available references.

In a previous article,[9] the efficacy of the method was shown on Dexcom SEVEN Plus data and using a relatively large number of highly accurate references (YSI). This favorable testing setup of Ref.[9] is that of our clinical studies testing the

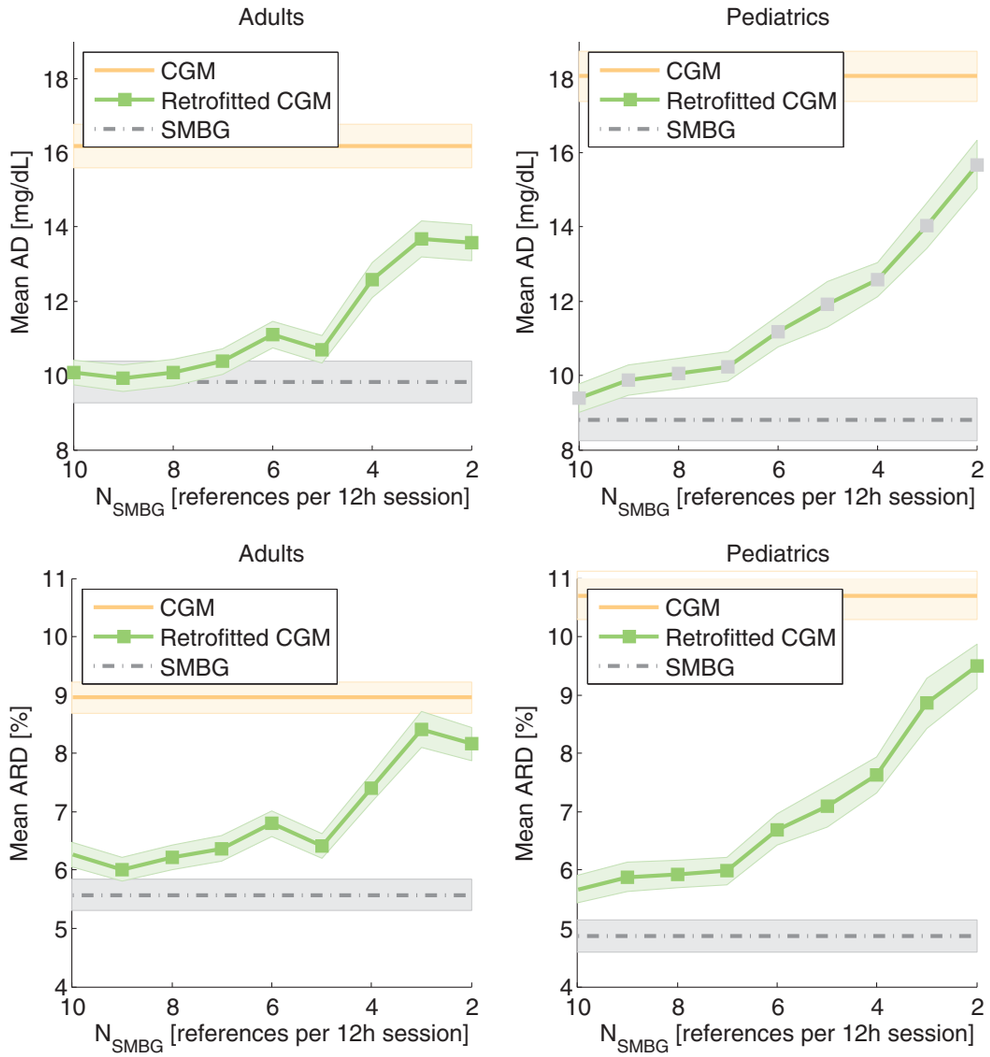

FIG. 3. Accuracy of retrofitted CGM as a function of the number of SMBGs provided to the method. The accuracy of the original CGM and of SMBGs is reported as a comparison. Accuracy is assessed by the mean absolute difference (mean AD) in the upper panels and by the mean absolute relative difference (mean ARD) in the lower panels. Shaded areas represent the 5%–95% confidence intervals on the means.

artificial pancreas system outside the hospital in semicontrolled environments (hotel studies, e.g., Ref.[15]). It remained to be investigated whether the retrofitting method is still beneficial in other more challenging setups, characterized by the availability of less and less accurate references, such as SMBGs. Furthermore, it was unclear if the newer generation of Dexcom sensors, already significantly more accurate than their predecessor Dexcom SEVEN Plus, could still be significantly improved by the retrofitting method.

The data reported in this article provide a positive answer to these open questions.

Despite the fact that Dexcom G5 is one of the most accurate sensors on the market, we showed that when five SMBG references are available in an ~12-h period, the retrofitting method can be profitably used offline to push further the accuracy of Dexcom G5 data by retrospective processing. The method allowed decreasing MAD and MARD of roughly 30%, bringing, for example, the average MARD value from the actual 9.0% to 6.4%. Note that this number of references was chosen since it is likely that at least five references in 12 diurnal hours are collected when the CGM sensor is used adjunctively to SMBGs, for example, two SMBGs for calibration plus three SMBG checks around mealtime per day. Indeed, five[4,7] SMBGs were collected from 07:00 to 19:00 by the patients in our artificial pancreas studies conducted in free-living conditions for 2 months[16] and 1 month.[17] More precisely, in 59.1% of the 12-h periods going from 07:00 to 19:00, the patients collected five or more SMBGs and only in 23.8% of these 12-h periods less than four SMBGs were performed.

Furthermore, we quantified the impact of the number of available SMBGs on the accuracy of the method and we

showed that the method is still able to bring a modest but statistically significant reduction of MAD and MARD in both populations even with only $N_{SMBG} = 2$ SMBGs per 12-h session. In particular, we tested the case when only two SMBGs requested for calibration were provided to the method, one collected at the beginning of the session and one 12 h after (end of the session) as per manufacturer guidelines. When used online, the information carried by the calibration SMBG can be used only to produce better CGM measurements after the calibration. On the contrary, a retrospective algorithm can use the calibration SMBG also to correct previous CGM readings (a posteriori correction). For instance, consider the case of Figure 1, lower panel. At 20:08, the CGM was recording 354 mg/dL. Shortly after, at 20:10, the CGM was calibrated with an SMBG = 269 mg/dL. Online, the SMBGs of 20:10 can be helpful only to correct the subsequent CGM reading. Retrospective techniques, instead, can use the 20:10 SMBGs to correct a posteriori also previous CGM. This last case ($N_{SMBG} = 2$ SMBG per 12-h session) is particularly relevant in view of the future possible use of the CGM as an alternative to SMBGs, the so-called nonadjunctive use of CGM, a possible future scenario.[10]

In summary, we showed that the algorithm can be used to retrospectively improve CGM data collected in free-living during both diurnal $\sim$12-h portions and nocturnal $\sim$12-h portions, although the benefit granted by the algorithm depends on the number of available SMBGs. An overall evaluation of accuracy improvement of the method when used in a 24-h portion that includes both a diurnal $\sim$12-h part (with more frequent SMBGs) and a nocturnal $\sim$12-h part (with less frequent SMBGs) is not possible on the available datasets. Another approximation introduced in the analysis is the uniform subsampling of SMBGs used to retrofit. In free-living nonadjunct CGM use, the SMBGs are collected in relation to clinically relevant events such as hypoglycemia, meals, and hyperglycemia correction, but the used dataset contained no information on these events. Therefore, a selection of SMBGs to be provided to the retrofitting method based on clinical events was not possible here, at difference with Ref.[9]

A last comment concerns the usability of the presented technique in an artificial pancreas context. Apparently, being a retrospective technique, the retrofitting algorithm cannot be used to improve real-time computation of an insulin dose. Nevertheless, the retrofitting algorithm could still be useful in an advanced, closed-loop control architecture, for example, AP system employing patient-specific models of glucose response to insulin to produce individualized control strategy.[7] In this setup, the retrofitting method could be used to improve the accuracy of CGM data before using them, together with insulin records, to learn/identify the patient-specific model.

Conclusions

Even when applied to one of the most accurate sensors currently available on the market, the Dexcom G5 sensor, the retrofitting method allows to further increase accuracy of the CGM trace by retrospective processing. When the CGM is used adjunctively to SMBGs, the benefit of retrofitting CGM traces is clear, while in the scenario of nonadjunctive CGM, the increase in accuracy is limited.

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Author Disclosure Statement

The authors are consultants of Dexcom, Inc., San Diego, CA. The authors hold patents and patent applications related to diabetes technology and, in particular, on the method presented here.

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Appendix

Appendix: Brief Description of the Retrofitting Algorithm

The retrofitting algorithm is a two-step procedure.

Step A: Retrospective Continuous Glucose Monitoring recalibration

Aimed to correct errors in continuous glucose monitoring (CGM) readings due to under/overestimation of true glucose values and drift in time due to changes in sensor sensitivity. Recalibration parameters are estimated taking into account and compensating the plasma to interstitial fluid glucose transportation delay.

Step B: Regularized Constrained Deconvolution

Recalibrated CGM values are still measurements of glucose concentration in the interstitial fluid and not in the blood. Moreover, no processing has been performed to reduce the noise. Step B processes the recalibrated CGM by exploiting also the available references to obtain an estimate of the blood glucose (BG) profile. The key features of this procedure are

- it compensates for the delay due to glucose transport from plasma to interstitial fluid by deconvolution;
- it exploits a physiological prior on the smoothness of the blood glucose profile to filter out the measurement noise; and
- it takes advantage of some self-monitoring blood glucose measurements (SMBGs) to improve the estimate of the BG signal. This is done by introducing the additional constraint that the estimated profile has to lie within the confidence interval of the SMBGs at the time in which an SMBG value is available.

Furthermore, a preprocessing step is performed to detect anomalous data and outliers.

For a detailed description of the method, with all the mathematical details, we refer the reader to Ref.[8]