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SYMPOSIUM

Continuous Glucose Monitoring Considerations for the Development of a Closed-Loop Artificial Pancreas System

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Abstract

Background:

Commercialization of a closed-loop artificial pancreas system that employs continuous subcutaneous insulin infusion and interstitial fluid glucose sensing has been encumbered by state-of-the-art technology. Continuous glucose monitoring (CGM) devices with improved accuracy could significantly advance development efforts. However, the current accuracy of CGM devices might be adequate for closed-loop control.

Methods:

The influence that known CGM limitations have on closed-loop control was investigated by integrating sources of sensor inaccuracy with the University of Virginia Padova Diabetes simulator. Non-glucose interference, physiological time lag and sensor error measurements, selected from 83 Enlite™ glucose sensor recordings with the Guardian® REAL-Time system, were used to modulate simulated plasma glucose signals. The effect of sensor accuracy on closed-loop controller performance was evaluated *in silico*, and contrasted with closed-loop clinical studies during the nocturnal control period.

Results:

Based on n = 2472 reference points, a mean sensor error of 14% with physiological time lags of 3.28 ± 4.62 min (max 13.2 min) was calculated for simulation. Sensor bias reduced time in target for both simulation and clinical experiments. In simulation, additive error increased time <70 mg/dl and >180 mg/dl by 0.2% and 5.6%, respectively. In-clinic, the greatest low blood glucose index values (max = 5.9) corresponded to sensor performance.

Conclusion:

Sensors have sufficient accuracy for closed-loop control, however, algorithms are necessary to effectively calibrate and detect erroneous calibrations and failing sensors. Clinical closed-loop data suggest that control with a higher target of 140 mg/dl during the nocturnal period could significantly reduce the risk for hypoglycemia.

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Abbreviations: (A1c) hemoglobin A1c., (AP) artificial pancreas, (BG) blood glucose, (CF) calibration factor, (CGM) continuous glucose monitoring, (CSII) continuous subcutaneous insulin infusion, (ePID) external physiologic insulin delivery, (FDA) Food and Drug Administration, (HBGI) high blood glucose index, (ISF) interstitial fluid, (LBGI) low blood glucose, (MARD) mean absolute relative difference, (SMBG) self-monitoring of blood glucose, (UVa) University of Virginia

Keywords: artificial pancreas, closed loop, continuous glucose monitoring, glucose sensor, hypoglycemia, insulin pump

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Introduction

The first consumer-based closed-loop artificial pancreas (AP) system suitable for continuous wear will likely employ interstitial fluid (ISF) glucose sensing and continuous subcutaneous insulin infusion (CSII) methods.[1] Current technology has advanced AP research from bedside monitoring to clinical studies with combinations of commercially available devices that can be worn on the body.[2] Although practical and comfortable for long-term wear, the subcutaneous-subcutaneous-based closed-loop system[3] introduces control challenges due to physiological time lag between ISF and plasma glucose concentration[4] and slow subcutaneous insulin kinetics. Some of the practical difficulties faced in integrating continuous glucose monitoring (CGM) and CSII components into a closed-loop system have been reviewed by Aye and colleagues.[5]

Three subcutaneous CGM devices have received Food and Drug Administration (FDA) approval and provide the CGM component for current closed-loop research platforms, for which a number of control algorithms have already been developed.[6] Clinical accuracy of the Medtronic Guardian and Paradigm® platforms,[7] the Dexcom SEVEN® Plus[8] and Abbott Freestyle Navigator®[9] have been widely published. Glucose sensors are evolving as are their manufacturing processes, with additional accuracy being achieved through calibration algorithm enhancements.[10,11] However, low error rates achieved in-clinic do not necessarily provide an acceptable level of reliability for automation, though several groups have reported sufficiently accurate CGM performance during closed-loop control. In particular, Hovorka and colleagues[12] demonstrated effective glucose regulation during the nocturnal period in a three-phase study, employing the Guardian system in one phase and the Navigator in the following two phases. The study reported accuracies of 10% for the Guardian monitor with YSI (YSI Inc., Yellow Springs, OH) calibrations every 6 h and 12% for the Navigator with finger stick calibrations using the Freestyle® meter. In a similar study, Castle and associates,[13] also utilizing the Guardian monitor in addition to the Dexcom SEVEN Plus system, revealed highly accurate sensor performances during closed-loop control. The combined data set resulted in a mean absolute relative difference (MARD) of 8.7% when calibrating with YSI samples close to every 6 h.

Clearly it is not practical to calibrate CGM devices with laboratory measurements outside the clinic, which has been the trend for closed-loop pilot studies, with the exception of Hovorka and colleagues[12]. As we progress toward outpatient studies that are more realistic and representative of how commercial systems will be utilized in the field, the study of closed-loop control with CGM devices that are calibrated by patient finger stick measurements using home blood glucose (BG) meters must become the standard. Therefore, in this article we focus primarily on how closed-loop control is affected by sources of error inherent in CGM devices. To study the effect of CGM error and imprecision, we analyzed *in silico* the current state-of-the-art subcutaneous glucose sensing. This is achieved by decomposing sensor signals to extract noise, artifact, and error characteristics resulting from standard measurement of blood glucose (SMBG) calibrations to impart to a type 1 diabetes mellitus simulator. Additionally, physiological time lags are estimated for the data set and are also included in the simulation. This *in silico* analysis is contrasted with results from two different closed-loop clinical studies where closed-loop performance based on CGM accuracy was analyzed.

Methods

The effect CGM limitations have on closed-loop control was analyzed *in silico* by incorporating the true characteristics of the Enlite™ sensor, the latest in Medtronic glucose sensing technology, into a glucose simulator. Noise and artifact samples plus sensor error measurements were acquired from an accuracy study evaluating the performance of the Enlite sensor over 6 days of use.[14] This non-glucose interference and sensor error, with the physiological time lag distribution calculated from the same data set, were incorporated into the FDA-approved University of Virginia (UVa)/Padova Diabetes Simulator.[15] A similar analysis of sensor error impact on control was compared for two closed-loop clinical studies with the Medtronic Sof-sensor™.

Simulation Framework

Simulator plasma glucose signals were transformed into an ISF glucose time series by first order filter expressed by **Equation 1**.

$$CGM(k) = e^{-\Delta t/T} \cdot \mathrm{CGM(k-1)} + (1 - e^{-\Delta t/T}) \cdot BG(k) \quad (1)$$

This filter has unity gain and physiological time lag T with sample time interval Δt; k is the current sampling

time. Time lag for a given profile was determined randomly from a normal distribution with mean and standard deviation (SD) parameters estimated from physiological time lags calculated for the Enlite data set. The ISF glucose signal was mixed with real noise and artifact acquired from the Enlite sensor. Noise signals were generated by band-limiting unprocessed 1 min sensor signals to >1.5 cyc/h by digital filtering. Most glucose information resides below this frequency. The filter gain (α) was set to the average calibration factor for the sensor duration to normalize the signal to mg/dl units described by **Equation 2**.

$$\alpha = \frac{\sum_n BG_n}{\sum_n isig_{n+\tau}} \quad (2)$$

In **Equation 2,** meter readings taken during the recording period (BG_n) were divided by sensor current (isig) values that have been low-pass filtered, and delayed by a time-lag correction factor (τ) to compensate for physiological time lag and filter group delay. Sensor error was introduced from real sensor inaccuracies to provide the residual sensor glucose signal, which is low pass filtered[16] prior to closed-loop control. Glucose regulation was performed with a proportional-integral-derivative control algorithm with insulin feedback.[17]

Sensor Error and Physiological Time Lag Estimation

Both sensor error and physiological time lag were derived from a clinical accuracy study of the Enlite glucose sensor. To measure sensor accuracy and analyze its effect on closed-loop control *in silico*, raw sensor tracings (n = 83) that were recorded using the Guardian REAL-Time monitor for sensors placed in the abdomen, were calibrated with a one-point routine. Calibrated sensor signals were compared with plasma glucose reference samples acquired every 15 min with the YSI 2300 STAT Plus™ Glucose and Lactate analyzer over a 10 h period. Calibration factor (CF) was calculated by the ratio of a single BG point to a time corrected (a fix delay to account for physiological and filter delays) sensor current value [$CF = BG_1/isig_{1+\tau}$]. The sensor current offset for calibration purposes was fixed at zero. By applying practical experience any CFs beyond the 3-7 mg/dl/nA range were rejected. The first YSI point was used for optimal calibrations by applying the first value prior to commencement of frequent sampling—only for later comparisons with BG meter calibration. To introduce sensor error at different glucose levels into the simulation, YSI samples were interpolated to 1 min resolution and error was estimated by the difference between interpolated reference glucose and the calibrated 1 min sensor signals. The error imparted to the simulated ISF glucose signal each minute is equal to the error for a particular sensor contiguous with simulator glycemia.

To identify physiological time lag for simulation purposes, a subset of Enlite sensors that are highly correlated with reference YSI samples ($r^2 > 0.94$) were processed. Time lag was derived from total lag, where known system delays from the digital filter design are removed. Total time lag is determined through identifying the time lag that maximizes the correlation between YSI and sensor current (isig) (**Equation 3**), similar to the approach used by Garg and colleagues.[18]

$$\max_T corr(isig, YSI) \quad (3)$$

Physiological time lag (T_{Ph}) is therefore the difference between total time lag (T) measured by cross-correlation and 3.5 min attributed to filter group delay (T_F).

$$T_{Ph} = T - T_F \quad (4)$$

Clinical Closed-Loop Studies

To contrast with *in silico* analysis, closed-loop control was assessed based on sensor performance during the nocturnal control period of two closed-loop studies. Both studies utilized the Medtronic external physiologic insulin delivery (ePID) system[17] with the Sof-sensor. This system provides a manual calibration routine with hand-entered YSI samples, and applies a linear regression method. The first closed-loop study[19] was in an adult population of 8 subjects (4 females; aged 44.8 ± 9.8 years; hemoglobin A1c (A1C) 7.2 ± 0.6%), and the second an adolescent group of 12 subjects (6 females; aged 15.8 ± 3.9 years; A1C 7.4 ± 0.6%) undergoing four cycles of vigorous treadmill walking for 15 min to attain a maximum heart rate of 65–70%, followed by a 5 min rest period. A controller target set point of 110 mg/dl was employed for the adult study and 120 mg/dl for the exercise study during the nocturnal period from 22:00 PM to 06:00 AM. The nocturnal period of each study was examined to remove the variable effects of daytime meals in order to focus on control-based sensor performance. This particular cohort undergoing prior physical activity provided sufficient variation with extremes seen in nocturnal glucose regulation, and is likely the most difficult population to control.

Analysis

Ten adult virtual patients were used for *in silico* analysis over a 24 h control period, which includes three meals of 75, 75, and 50 g of carbohydrate composition, starting at 7:00 AM, 12:00 PM and 6:00 PM, respectively. The proportional-integral-derivative control algorithm with insulin feedback closed-loop controller input was the simulated ISF sensor glucose signal previously described. Physiological time lag was constant for each virtual subject, which was randomly selected from the time lag distribution calculated for the data set. Each ISF glucose sensor signal included noise, artifact, and sensor error generated from one sensor download, which was applied to all virtual patients for each simulator iteration. Simulator plasma glucose output provided the resultant glycemia used to measure controller performance.

Similarly, reference YSI samples were used to measure closed-loop controller performance during the 8 h nocturnal period for each clinical study. Sensor performance was compared to the resultant closed-loop controller performance for each simulation and clinical experiment. Sensor performance was measured by mean sensor bias, interquartile bias range and MARD. In each investigation, controller performance was evaluated based on percentage of time spent in range, time spent below 70 mg/dl and above 180 mg/dl. Additionally, low and high blood glucose indices[20,21] were used to assess the risk of severe hypo- and hyperglycemia for both simulated and closed-loop clinical data sets.

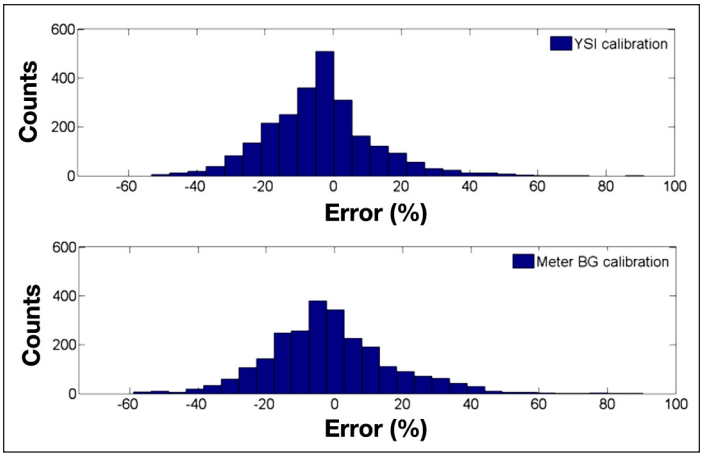

Figure 1. Error distribution for YSI and meter BG calibrations.

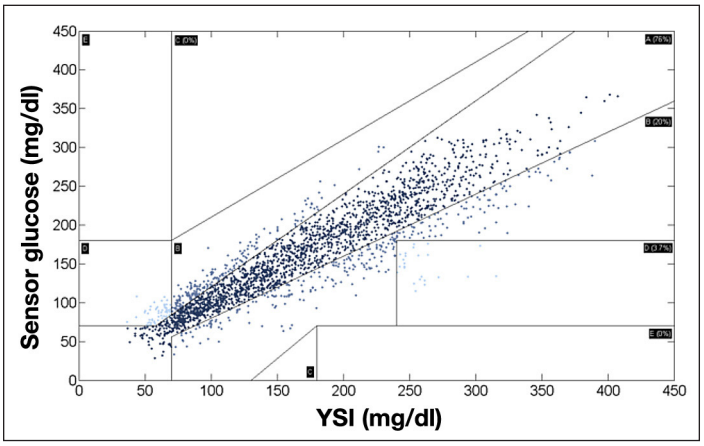

Figure 2. Clarke error grid analysis for one-point meter BG calibration for error model development.

Results

In this section, we present an analysis of the Enlite accuracy study data that includes sensor error and physiological time lag measurements to be used as parameters in the UVa/Padova simulator. The resultant effect that sensor accuracies have on glycemic control are compared for both *in silico* analysis with the UVa simulator and for clinical studies using the ePID system.

Sensor Analysis

Based on 2472 evaluation points, one-point calibrations with YSI and meter BG reference values produced MARDs of 12.31% and 14% ($P < 0.0001$), respectively. Error distributions for each method are illustrated in **Figure 1**. Only sensor errors generated by SMBG calibration are adopted to develop lookup tables to apply to simulated ISF glucose signals. A Clarke error grid analysis for the 83 sensors is shown in **Figure 2**, where 96% of points populate the A+B zones. No points exist in either C or E zones, but a number of the 3.7% of points are in the D zone, particularly those with a sensor glucose exceeding the control target set-point of 120 mg/dl, could present additional challenges.

Noise and Time Lag Analysis

To evaluate the influence of time lag and additive sensor noise on closed-loop control, each virtual patient was processed 16 times with incremental time lags ranging from 0–15 min, both without additive noise, and in the presence of noise based on one sensor noise sample. The effects are illustrated in **Figures 3** and **4**, where high blood glucose index (HBGI) is seen to increase with greater time lag by approximately 0.3 both in the presence and absence of noise over the 15 min range. However, time lag has no noticeable effect on low blood glucose (LBGI), with the index reflecting no risk of severe hypoglycemia. While HBGI increases by approximately 0.6 with additive noise, LBGI decreases to almost zero biasing control toward a higher glucose range. Time in

range is illustrated in **Figure 4**, where time in range decreases with increased physiological lag, but with a marginal increase of less than 1% in the hyperglycemic range, and no difference <70 mg/dl. Noise decreases the total time spent in range by about 2% by increasing time above 180 mg/dl with no influence on the time below 70 mg/dl. The population glycemic profiles are illustrated in **Figure 5** for the maximum time lag of 15 min.

Closed-Loop Performance in silico

A physiological time lag distribution with (mean ± SD) 3.28 ± 4.62 min (p = 0.91; χ^2 goodness of fit) was calculated for 59 Enlite sensors with a significant correlation to reference YSI samples (r^2 > 0.94). Performance metrics for both sensor and closed-loop control are presented in **Table 1** for 12 sensor profiles. Ten sensor error profiles (1–10) were randomly selected from 83 sensor downloads, with aggregate MARD of 15.4%, and an additional two sensor error files were selected (11 and 12) for sensors with the greatest error and greatest mean bias at the high and low glucose range, respectively. Control performance measures are calculated for the ensuing average glycemic profile, which results from the corrupting factors of each sensor download, applied to the 10 virtual patients in turn. The sensor set has an aggregate MARD of 18.5% and mean bias of -11.7 mg/dl. Average LBGI:HBGI is 0.1:6.1 for sensor-based control compared to 0:5.0 for control with plasma glucose signals, demonstrating an average of 5.8% less time in target, with an increase of 0.2% and 5.6% of time <70 mg/dl and >180 mg/dl, respectively. Performance based on sensor 12 is most notable with a bias of -61.2 mg/dl, producing the least time in range, with 55.1% of time in hyperglycemia, generating a HBGI of 12.

Closed-Loop Performance In-Clinic

Closed-loop performance metrics are presented in **Tables 2** and **3** based on sensor accuracies for adult and exercise clinical studies, respectively. The same manual calibration routine using reference YSI samples and Sof-sensor was applied in both studies producing similar sensor accuracies. Control in the adult population without any challenges produced extremely low LBGI:HBGI values of 0.56:0.88 respectively, with nearly 100% of time spent in range. Sensor accuracy was excellent where the highest MARD was 12.8% and greatest mean biases were -15.8 mg/dl and -9.6 mg/dl, producing the highest HBGI values of 1.7 and 2 without resulting in hyperglycemia.

In the exercise study, one subject suffered a hypoglycemic event requiring a rescue (<60 mg/dl) during the

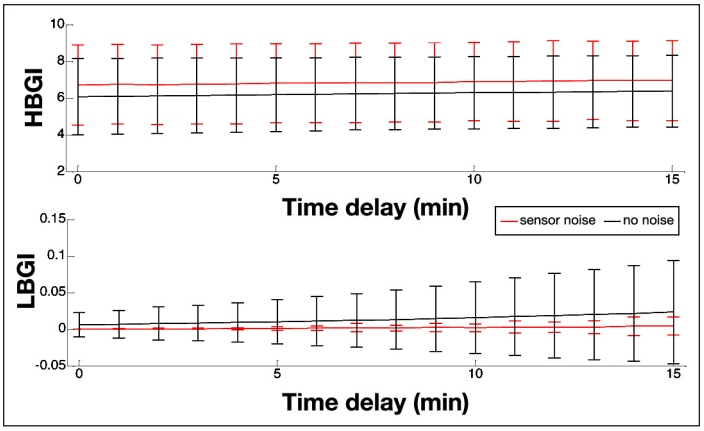

Figure 3. Twenty-four hours of *in silico* results showing changes in LGBI and HGBI for a range of physiological time lags with additive sensor noise. The red and the black bars depict ± SD of the population results with and without noise, respectively.

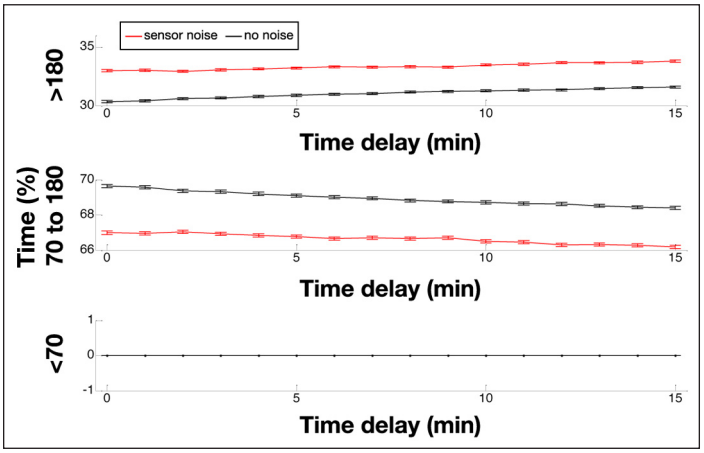

Figure 4. Twenty-four hours of *in silico* results showing percentage time in range, hypoglycemia, and hyperglycemia with increased time lag and additive noise. The red and black bars depict ± SD of the population results with and without noise, respectively.

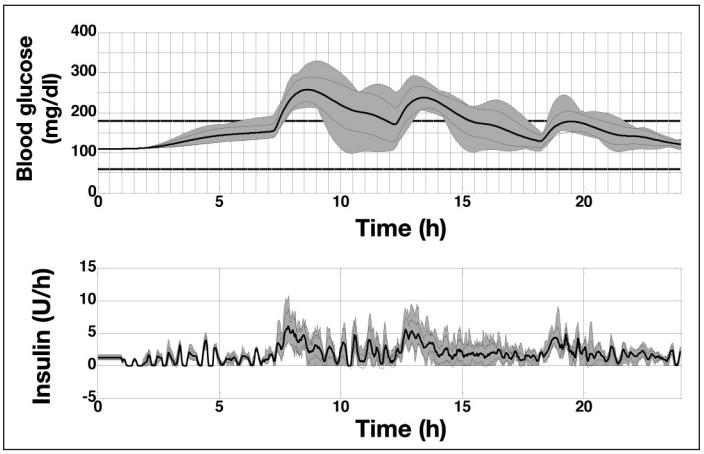

Figure 5. *In silico* population result of simulated glucose profile with sensor interstitial glucose and insulin delivery. The average, SD, and minimum-maximum values are depicted by the black, dashed, and grey envelope, respectively.

closed-loop night following exercise with a moderate LBGI of 2.5, which is reasonably low due to the rescue response. Sensor 1 produced the greatest LBGI measure of 5.9, which is in the high-risk category for severe hypoglycemia. Additionally, this sensor had the highest MARD of 16.3% with a bias of 12.6 mg/dl—although never reaching 60 mg/dl. Sensor 10 had the second highest MARD of 15.1%, with the greatest bias of 12.7 mg/dl producing a high LBGI of 3.4. The average sensor performance for the study was excellent with over half of the subjects spending 100% of time-in-control for the entire overnight period, which resulted in an average LBGI:HBGI (1.12:1.37) in the low risk category.

To simulate the anticipated effect that higher set points will have on LBGI and HBGI metrics, clinical data was reanalyzed with the glucose distribution shifted to higher glucose levels in incremental steps of 1 mg/dl, demonstrated in **Figure 6**. Analysis shows the decrease in risk of severe hypoglycemia with higher set points.

Table 1.
Simulation Study (24 h period) Performance Measures for 12 Sensor Error Profiles[a]

Sensor	Bias (mg/dl)	SD (mg/dl)	IRQ (mg/dl)	MARD (%)	LBGI	HBGI	Time in range (%)	Time <70 mg/dl (%)	Time >180 mg/dl (%)
1	1.6	14.8	22.1	10.0	0.2	4.1	78.2	0.5	21.2
2	-27.0	18.4	30.4	12.1	0.0	6.8	66.8	0.0	33.2
3	-32.2	20.1	34.1	17.7	0.0	9.4	57.1	0.0	42.9
4	-49.6	23.3	22.4	22.6	0.0	9.7	56.9	0.0	43.1
5	-9.5	18	22.6	8.6	0.0	5.3	72.6	0.0	27.4
6	-4.3	29.9	54.7	18.1	0.2	3.7	78.8	0.3	20.9
7	-26.5	11.1	11.6	20.0	0.0	7.9	60.1	0.0	39.9
8	29.8	11.9	17.3	24.1	0.4	2.2	87.7	0.3	12.0
9	8.2	8.4	6.7	7.2	0.0	4.6	76.4	0.0	23.6
10	-15.0	27.2	34.7	12.8	0.0	5.9	69.9	0.0	30.1
11	45.0	15.1	17.7	34.7	0.6	1.7	90.6	1.0	8.5
12	-61.2	38.3	36.1	34.3	0.0	12.0	44.9	0.0	55.1
μ	-11.7	14.8	25.9	18.5	0.1	6.1	70.0	0.2	29.8
BG	**0.0**	18.4	0.0	0.0	0.0	5.0	75.8	0.0	24.2

[a] IRQ and BG stand for interquartile and blood glucose measurements without sensor error or noise, respectively.

Table 2.
Clinical Study Summary Performance Statistics for Adults during Overnight Closed-Loop Control[a]

Subject	Bias (mg/dl)	SD (mg/dl)	IRQ (mg/dl)	MARD (%)	LBGI	HBGI	Time in range (%)	Time <70 mg/dl (%)	Time >180 mg/dl (%)
1	-4.1	7.1	8.6	4.1	0.0	0.8	100.0	0.0	0.0
2	7.5	6.3	10.5	9.0	2.1	0.6	100.0	0.0	0.0
3	-2.6	17.3	24.5	12.8	0.4	0.8	100.0	0.0	0.0
4	-8.1	12.0	12.8	9.5	0.1	0.3	100.0	0.0	0.0
5	-3.6	3.2	5.8	3.6	0.2	0.8	100.0	0.0	0.0
6	-15.8	8.1	11.6	11.7	0.0	1.7	100.0	0.0	0.0
7	8.2	6.5	8.7	8.0	0.4	0.1	100.0	0.0	0.0
8	-9.6	22.2	30.5	11.4	0.7	2.0	87.5	0.0	12.5
μ	-3.0	-3.5	14.5	8.8	0.56	0.88	98.4	0.0	1.6

[a] IRQ and BG stand for interquartile and blood glucose measurements without sensor error or noise, respectively.

Table 3.
Clinical Study Summary Performance Statistics for Adolescents during Overnight Closed-Loop Control[a]

Subject	Bias (mg/dl)	STD (mg/dl)	IRQ (mg/dl)	MARD (%)	LBGI	HBGI	Time in range (%)	Time <70 mg/dl (%)	Time >180 mg/dl (%)
1	12.6	12.6	10.0	16.3	5.9	0.2	53.3	46.7	0.0
2	-8.9	-8.9	9.0	8.6	2.5	0.8	88.2	11.8	0.0
3	3.1	3.1	9.8	11.4	0.3	0.8	100.0	0.0	0.0
4	-2.9	-2.9	16.8	7.2	0.0	4.3	81.3	0.0	18.8
5	-5.1	-5.1	13.9	5.8	0.0	1.4	100.0	0.0	0.0
6	9.5	9.5	11.1	8.8	0.1	0.2	100.0	0.0	0.0
7	-5.8	-5.8	8.4	4.8	0.0	0.8	100.0	0.0	0.0
8	-3.8	-3.8	40.9	14.6	0.1	6.2	62.5	0.0	37.5
9	2.6	2.6	5.3	5.2	0.4	0.2	100.0	0.0	0.0
10	12.7	12.7	9.1	15.1	3.4	0.0	81.3	18.8	0.0
11	-1.9	-1.9	6.0	2.6	0.1	0.8	100.0	0.0	0.0
12	-3.6	-3.6	25.3	12.2	0.9	0.7	100.0	0.0	0.0
μ	0.6	0.7	15.2	9.3	1.12	1.37	88.9	6.4	4.7

[a] IRQ and BG stand for interquartile and blood glucose measurements without sensor error or noise, respectively.

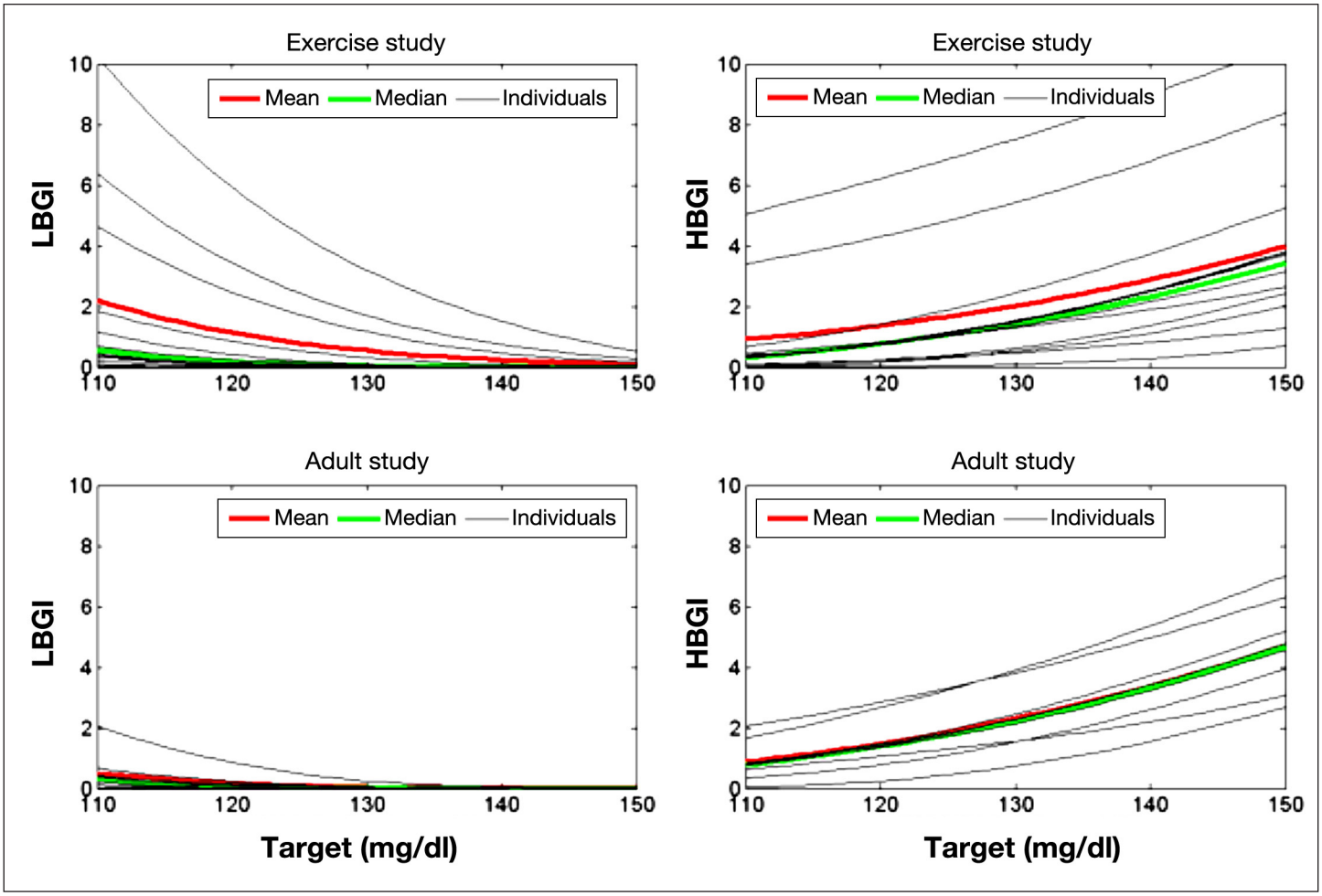

Figure 6. Variation in LBGI:HBGI with simulated increments to glucose target set point.

Based on this analysis, simulated changes in set point reduce LBGI to close to zero at approximately 140 mg/dl with an insignificant change of <1 to HBGI.

Discussion

The performance difference between YSI and meter calibration was less than 2%. A greater error margin was expected, but by simply imposing CF limits, the potential for significant error was averted. This marginal difference may be the result of careful finger stick measurements taken in the clinic prior to frequent sampling. Sensor calibrations produced a MARD of 14%, which is considered reasonable. However, the tails of the distributions of **Figure 1** have outliers of 58% to 80%. Such errors can appear at the extremes if a sensor is under- or over-reading and are not comparable to points that reside in the upper E zone of the Clarke error grid. In such cases, the error will likely decrease as glucose moves closer to the middle of the glycemic range.

The time lags introduced are not pure time delays but rather simulated physiological time lags involved in the diffusion of the blood glucose from the plasma to the subcutaneous tissue. It was observed that time lag had minimal effect on closed-loop control performance *in silico*, where a greater influence was expected with the inclusion of meal responses. Additive noise had the effect of biasing control high, where HBGI increased with some reduction in LBGI, thereby further decreasing the risk of severe hypoglycemia. This was an interesting finding where one may expect the risk of a severe adverse event to increase for both metrics.

In silico analysis revealed a strong correlation between hyperglycemia, HBGI, and sensors that under-read with negative bias. The reverse is true for sensors that over-read with a positive bias. Similarly, there is a strong correlation among highly biased sensors, MARD, and poor glucose control. Sensor 12 provides a good example of how sensor bias can affect glucose control. In this case the sensor was calibrated during a glucose rate-of-change of 2.13 mg/dl/min. As a result, MARD (34.3%) and mean bias (-61.2 mg/dl) are significant, resulting in 55.1% of the overnight period above 180 mg/dl. Conversely, sensor 11 produced reasonable control with a high mean bias and error, and sensor 9 resulted in superior control to that achieved with plasma glucose readings. Improved control with sensor 9 is a direct result of the sensor moderately over-reading, thereby making the controller more aggressive with a relatively conservative control setting.

We ran simulations with noise and errors that were extracted from the new Enlite sensor and we added results from clinical trials that were conducted with the Sof-sensor. The purpose of this contribution was to show that closed loop is feasible with the current sensor technology and, therefore, the overnight clinical trials results are presented to reinforce our hypothesis. Evidently, with no challenges prior to the overnight period, excellent control is achievable, which was demonstrated in the clinical adult study with nearly 100% time in target. Physical activity obviously stresses the system by producing greater variability and, in one instance, a hypoglycemic event that required rescue during the overnight period following exercise. It should be noted that the open-loop control arm for this study generated 14 hypoglycemic events for the same period. Once again, control was excellent with a few outliers, where LBGI reached a high level (5.9) in one case and reached moderate levels (2.5 and 3.4) in two cases. However, in the remaining nine subjects, a low risk of severe hypoglycemia was maintained with over half of the subjects spending 100% time in target. It is hypothesized that the exercise-induced hypoglycemic events could be further mitigated with a higher set point as demonstrated in **Figure 6**. Here it is evident that with a lower set point of 110 mg/dl, LBGI can increase to a more serious category with moderate risk of severe hypoglycemia, but decreases to almost zero at 140 mg/dl. We performed a similar exercise *in silico* to validate that variability is not overly affected by an increase in set point, and observed a SD increase of only 4 mg/dl.

Although the exercise study used a different sensor, the system was calibrated manually with YSI samples producing a MARD of 10.9%. This is significantly better than one-point meter calibrations of 14%. We chose the one-point method to create greater variability intentionally and demonstrate the effect of bias. While sensor performance typically tracked control performance, in one example, the control sensor for the exercise experiment that suffered a hypoglycemic event below 60 mg/dl requiring a rescue had a low MARD and negative bias. This demonstrates that good sensor performance is not always enough to guarantee no incidence of severe hypoglycemia.

Conclusions

The analysis presented demonstrates the need for reliable CGM for closed loop-control and highlights how poorly performing or inadequately calibrated sensors can adversely affect control performance. High LBGI:HBGI

values correspond to percentages of time spent in low and high glycemic ranges and are closely related to sensor bias. Bias is often a consequence of calibration—common when calibrating during fast-changing glucose trends as demonstrated in the simulation example. Erroneous calibrations can cause adequate sensors to under- or over-read. Therefore, any degree of automation requires good sensor performance with optimal calibration error detection. Calibrations should be constrained to acceptable error limits within the necessary tolerance of the closed-loop system. A reduced need for calibration will help improve the robustness of a system. In our investigations, average CF for the Enlite sensor was known and, therefore, reasonable ranges could be established where measurements failing to meet this criterion suggest erroneous BG or sensor readings. The calibration algorithms in a closed-loop system should possess high sensitivities to calibration error even if they generate bothersome alerts.

The unique closed-loop system's response to calibration errors should be evaluated in-clinic to determine robustness to error and to determine safe system limits. Sensor fault detection is also crucial to ensure that control is always provided by a fully functioning sensor, and therefore must detect faults in an adequate time to prevent over-delivery. On average, closed-loop control with current CGM devices is acceptable. However, there is always the risk of a severe hypoglycemic event resulting from over-delivery, even with properly functioning sensors. Dual hormone systems[13,22] could provide a partial solution to over-delivery, but can also include additional risk if relied upon and introduce additional engineering complexity. A solution suggested in our analysis is to have less aggressive targets, where based on the data presented, a set point of 140 mg/dl could significantly reduce the risk of severe hypoglycemia with an acceptable increase in time spent at higher glucose ranges. Closed-loop control has the potential to significantly improve glycemic variability and safety through a reduction in the incidence of hypoglycemia. However, it is unknown how significant the improvement must be over standard-of-care for the automated system to be commercialized.

Disclosures:

D. Barry Keenan, Benyamin Grosman, Harry Clark, Anirban Roy, Rajiv V. Shah and John J. Mastrototaro are employees of Medtronic MiniMed. Stuart A. Weinzimer is an employee of Yale University and a consultant to Medtronic.

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