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Clinical Assessment and Mathematical Modeling of the Accuracy of Continuous Glucose Sensors (CGS)

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Abstract— **In the treatment of diabetes, CGS calibration, time lag, and random errors influence the clinical glucose control decisions based on CGS output. These inaccuracies are determined by three main factors: quality of calibration, physiology, and sensor engineering. Simulated re-calibration and a diffusion model of blood-to-interstitial glucose transport allow the separation of these sources of inaccuracy. The methods are illustrated by data for 39 subjects with Type 1 diabetes collected during hyperinsulinemic euglycemic/hypoglycemic clamp by Minimed CGMS™ (Medtronic, Northridge, CA). The continuous glucose error-grid analysis (CG-EGA) was used to evaluate sensor inaccuracy from a clinical point of view.**

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I. Introduction

The purpose of CGS is to provide feedback directing clinical decisions about the behavioral or automated control of diabetes. It is important, however, to emphasize that most contemporary CGS yield BG estimates via sampling of interstitial fluid. Such estimates are the product of at least two consecutive steps of approximation: 1) Blood-to-interstitial glucose (BG-to-IG) transport, and 2) Deduction of BG values from IG-related electrical current recorded by the sensor. As a result, although CGS technology has made dramatic strides [1, 2, 3], the development of accurate and reliable CGS devices continues to face a number of significant challenges in terms of calibration, sensitivity, stability, and the physiological time lag between blood and interstitial glucose concentration [4, 5, 6, 7]. The difference between BG and CGS readings is due to both physiology [8, 9], and sensor calibration, noise, and engineering. The physiological time lag and gradients are changing dynamically with time, with BG levels, and across subjects, but the direct frequent in vivo sampling of IG is extremely difficult [7]. Consequently, the evaluation of engineering performance of CGS is left with a central problem: separating the portion of BG/CGS error due to calibration, sensor noise, and BG/IG gradient. A reasonable method of performing such a separation would be to use a simulation model investigating the effect of calibration, combined with a mathematical approximation of IG – a surrogate interstitial glucose (SIG).

II. Methods

We decompose sensor error in two sequential steps described in detail below: Step 1 - using all available reference BG data we first re-calibrate the sensor to achieve a "perfect" calibration, which separates errors due to sensor calibration; Step 2 - using a diffusion model and re-calibrated sensor data from Step 1 we estimate the parameters of a diffusion model, which further separates errors due to BG-IG transport. The residual error is attributed to random sources.

A. Illustrative Data

Thirty-nine subjects with type TIDM participated in the study: average age 42.5 years (SD=12), average duration of T1DM 21.6 years (SD=9.4), average HbA1c = 7.4% (SD=0.8), 16 males. The study was approved by the University of Virginia IRB. Subjects were admitted to the General Clinical Research Center (GCRC) in the evening prior to the study and their BG levels were controlled overnight within euglycemic range (100-150 mg/dl, 5.5-8.3 mmol/l). The Minimed CGMS™ was attached to each subject and was calibrated during the study in accordance with the manufacturer's instructions. All CGMS™ were inserted in the abdomen. Hyperinsulinemic clamps were performed in the morning. Each clamp used constant insulin infusion rate of 1mU/kg/min and variable glucose infusion rate to achieve and maintain BG levels at approximately 110 mg/dl (~6mmol/l). Subsequently, the glucose infusion rate was reduced to permit a controlled decline in BG of approximately 1mg/dl/min until BG reached 50mg/dl (~2.8mmol/l). Glucose infusion was then resumed to allow a recovery to normal glucose levels. Arterialized blood was achieved by warming the hand to 50^0C and was sampled every 5 minutes for reference BG levels. To allow for insulin to reach its steady state effect, the first 15 minutes of data after the beginning of infusion were ignored. CGMS™ readings were synchronized with reference BG.

B. Step 1: Sensor Re-Calibration

It is intuitively clear that the accuracy of sensor calibration depends on the rate of BG change and perhaps on the BG value at the moment of calibration. Assuming that calibration is performed at a steady BG level (a condition generally required by sensor manufacturers), it is also reasonable to

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expect that if two calibration points are taken at about the same BG level, the quality of calibration would be *lower* than if these points were taken at different BG levels. The reason behind this premise is that a calibration function would perform better if its input has certain variance, as opposed to two repeated calibrations at the same BG level. We have simulated re-calibration of the sensor using two reference BG values taken during the clamp study described above, and we expressed sensor error as a function of the difference between these two values. The simulated re-calibration used the standard linear calibration function of the CGMS. The mean absolute error (MAE) of the sensor resulting from re-calibration was compared to the sensors' own MAE displayed during the experiment and to the MAE achieved by a "perfect" calibration, which used all available reference BG values to estimate the calibration function.

C. Step 2: Modeling BG-to-IG transport: Surrogate interstitial glucose (SIG)

Because glucose is a relatively small molecule, it is widely supposed to diffuse freely across the capillary wall [5]. Adipose tissue is highly vascularized, and the interstitial fluid occupies a relatively thin layer between cells [8]. This means that no volume element is very far from a cell surface, nor is it very far from a capillary wall. Hence, uptake and diffusion of glucose in the IG can be assumed to be relatively uniform, without a significant local gradient. As previously reported [9, 13, 14], the dynamics of glucose diffusion and uptake can be described as follows:

$$(1)\quad \frac{d(IG)}{dt} = \beta(BG(t) - IG(t)) - \alpha IG$$

Equation (1) assumes that the rate of removal of glucose from the interstitial fluid is proportional to IG (with a rate parameter α) and that the movement of glucose from the blood to the interstitial fluid (or vice versa) is passive diffusion and hence is proportional to the gradient (with a rate parameter β). Since there are no other apparent sources or sinks of glucose in the interstitium, equation (1) describes the net change in IG via two idiosyncratic parameters (α,β). The parameters were estimated via numerical integration of equation (1) using reference BG values and re-calibrated sensor readings from Step 1. This identified a continuous approximation of each person's IG concentration, i.e. SIG.

D. Clinical Evaluation of CGS Accuracy: Continuous Glucose Error-Grid Analysis (CG-EGA)

The clinical utility of CGS depends on a sensor's ability to provide sufficiently accurate and timely information for the adjustment of the treatment of diabetes. Currently, treatment adjustments are generally behavioral, depending on a person's reaction to the feedback from the sensor; automated closed-loop devices are under research and development. In both behavioral and automated treatment, the clinical decision depends not only on the BG value reported at the moment, but also on the direction and rate of BG change. Most importantly, the clinical treatment decision is very different in states of hypoglycemia, euglycemia, or hyperglycemia. For this reason, uniform measures of accuracy, such as average absolute or relative error, which do not differentiate specific clinical situations, are not applicable to the assessment of CGS clinical accuracy. In order to account for the clinical specifics of CGS information, we have introduced the CG-EGA, which quantifies point and rate accuracy of CGS in three distinct clinical zones: hypoglycemia, euglycemia, and hyperglycemia, taking into account the therapy adjustment errors that would be due to a sensor's erroneous information [10]. The CG-EGA is based on the original Clarke Error-Grid Analysis [11, 12], which divides the errors of BG estimation into clinically meaningful zones. The assumptions behind the zone definition are as follows: (i) Accurate A-zone: A sensor within 20% of reference, of rate of change within 1 mg/dl/min from the main diagonal is considered accurate; (ii) C-zone – sensor information, which could lead to over-treatment; (iii) D-zone - the sensor fails to detect that significant glycemic events or rate of change indicated by reference BG; (iv) E-zone (erroneous reading) the sensor display readings that are opposite to the reference, and (v) B-zone (benign errors). Given these zone definitions, the CG-EGA of sensor accuracy consists of three steps: (i) Rate Error-Grid Analysis (R-EGA), (ii) Point Error-Grid Analysis (P-EGA), and (iii) Combining P-EGA and R-EGA into sensor accuracy assessments within three clinically meaningful regions: hypoglycemia defined as BG <= 70mg/dl (3.9 mmol/l); euglycemia, and hyperglycemia defined as BG > 180mg/dl (10 mmol/l). This stratification is necessary because different BG levels require different clinical interpretation of the combination R-EGA + P-EGA.

III. RESULTS

A. Total Sensor Error

Figure 1 presents the three signals considered in this paper (averaged across all subjects): reference BG, SIG, and sensor readings. It is evident that SIG ameliorates most of the sensor error during hypoglycemia, suggesting that the error is primarily due to calibration. Table 1 (panel A) presents the overall CG-EGA accuracy of Minimed CGMS™ during the experiment. The clinically accurate sensor readings were 50.0% during hypoglycemia and 96.4% during euglycemia. The large difference between these percentages is primarily due to the more demanding clinical accuracy standards during hypoglycemia events: while during steady euglycemic state there is a large clinical tolerance for errors, during clinically dangerous conditions, the sensor should meet higher standards in order to provide accurate feedback for treatment decisions. The CG-EGA reflects this distinction. Further, the MAE and the mean absolute percent error (MAPE) are included in Table 1 and stratified by BG range as well.

B. Step 1 - Sensor errors resulting from calibration

The sensor calibration during the experiment was always done in periods of steady BG kept at euglycemia, thus the influence of BG rate of change was minimal. Figure 2

illustrates the influence of BG differential between two calibration points on the quality of calibration: the X-axis of presents the distance between two simulated calibration points in BG units (mg/dl); the Y-axis presents MAE of the sensor output, given this two-point calibration. It is evident that MAE is high if the two calibration BGs are close by value, is rapidly decreasing when the difference approaches 20 mg/dl, and is slowly decreasing after that. The upper horizontal line in Figure 2 represents the MAE of sensor's own calibration; the lower horizontal line represents the MAE resulting from a "perfect" calibration using all available reference points. It is evident that two calibration BGs that are >40mg/dl apart would achieve "nearly-perfect" results. Table 1 (panel B) presents the CG-EGA, MAE and MAPE of a sensor re-calibrated by two reference BGs that are 30 mg/dl apart, a clinically reasonable distance. It is evident that a calibration performed at sufficiently different BG levels yields a very significant improvement is sensor accuracy, e.g. increase from 50% to 86.7% of A-zone readings in the CG-EGA.

C. Step 2 - Physiology-based BG-to-IG sensor errors

Panel C of Table 1 presents the CG-EGA, MAE and MAPE of the SIG vs. BG estimated after sensor re-calibration. It is evident that the "accuracy" of SIG following BG fluctuation is quite high – nearly 100%, which signifies an excellent theoretical limit for potential sensor accuracy. The residual error is explained by factors other than calibration.

IV. CONCLUSIONS

A combination of a clinical accuracy assessment method, simulation of calibration error, and a mathematical model of BG-to-IG glucose dynamics provides a comprehensive assessment of sensor accuracy and time lags during critical events, such as hypoglycemia, and during steady euglycemic state. It becomes evident that inaccuracies due to physiology are similar during hypoglycemia and euglycemia, while calibration and other errors differ dramatically. In particular, the clinical message from this analysis is that reference BG points used for sensor calibration should be separated not only in time, but also by a BG differential of at least 30 mg/dl.

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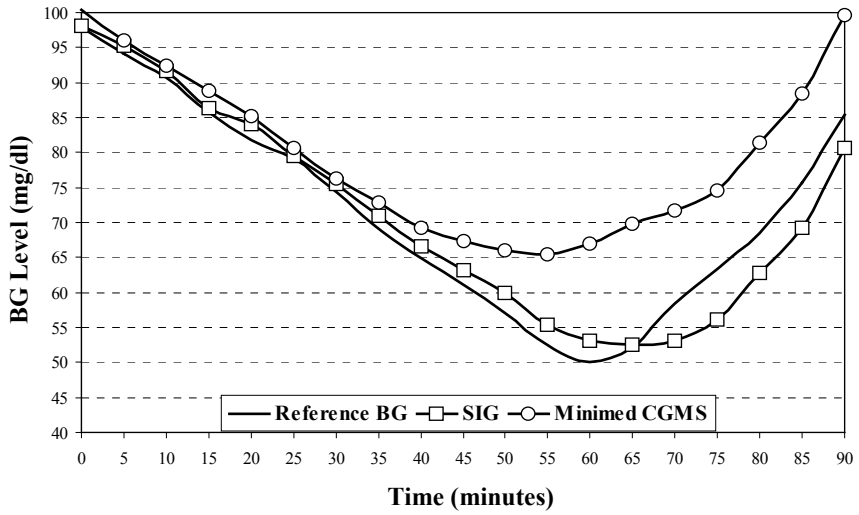

Figure 1: Reference BG, surrogate interstitial glucose (SIG), and sensor readings during induced hypoglycemia.

	CG-EGA Accuracy Results			MAE mg/dl	MAPE %
Zone	Accurate %	Benign %	Error %		
Panel A: Original Calibration					
Hypoglycemia / Euglycemia	50 / 96.4	0 / 0.2	50 / 3.4	27.9 / 20.4	50.1 / 22.6
Panel B: Calibration at BG levels that are 30 mg/dl apart					
Hypoglycemia / Euglycemia	86.7 / 93.4	4.8 / 2.6	8.5 / 3.9	10.9 / 13.6	19.8 / 14.9
Panel C: BG vs. SIG					
Hypoglycemia / Euglycemia	100 / 99.4	0 / 0.6	0 / 0	4.9 / 7.9	8.4 / 8.4

Table 1: Sequential improvement in sensor accuracy by recalibration and elimination of BG-to-IG time lag as assessed by CG-EGA, Mean absolute error (MAE), and Mean absolute percent error (MAPE):

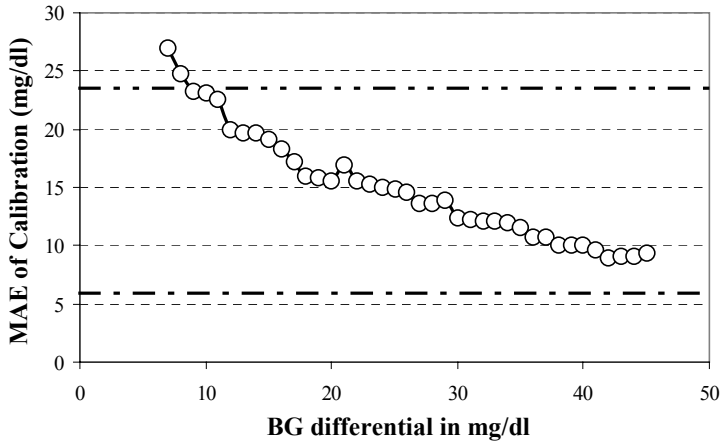

Figure 2: Accuracy of Calibration vs. BG Differential between the calibration points.