Statistical Tools to Analyze Continuous Glucose Monitor Data

William Clarke, M.D. and Boris Kovatchev, Ph.D.

Abstract

Continuous glucose monitors (CGMs) generate data streams that are both complex and voluminous. The analyses of these data require an understanding of the physical, biochemical, and mathematical properties involved in this technology. This article describes several methods that are pertinent to the analysis of CGM data, taking into account the specifics of the continuous monitoring data streams. These methods include: (1) *evaluating the numerical and clinical accuracy of CGM*. We distinguish two types of accuracy metrics—numerical and clinical—each having two subtypes measuring point and trend accuracy. The addition of trend accuracy, e.g., the ability of CGM to reflect the rate and direction of blood glucose (BG) change, is unique to CGM as these new devices are capable of capturing BG not only episodically, but also as a process in time. (2) *Statistical approaches for interpreting CGM data*. The importance of recognizing that the basic unit for most analyses is the glucose trace of an individual, i.e., a time-stamped series of glycemic data for each person, is stressed. We discuss the use of risk assessment, as well as graphical representation of the data of a person via glucose and risk traces and Poincaré plots, and at a group level via Control Variability-Grid Analysis. In summary, a review of methods specific to the analysis of CGM data series is presented, together with some new techniques. These methods should facilitate the extraction of information from, and the interpretation of, complex and voluminous CGM time series.

Introduction

CONTINUOUS GLUCOSE MONITORS (CGMs) generate data streams that have the potential to revolutionize the opportunities for reducing the extremes of blood glucose (BG) levels that characterize glycemia in type 1 diabetes mellitus. Such data, however, are both voluminous and complex, and their analysis requires an understanding of the physical, biochemical, and mathematical principles and properties involved in this new technology. Other articles have described the physical and biochemical parameters associated with CGMs. This article summarizes the mathematical properties of CGM data and the statistical tools available to analyze both their accuracy and their clinical interpretation.

Before proceeding with the description of the methods available for analysis of CGM data, it is important to note that the *basic unit for most analyses is the glucose trace of an individual*, i.e., a time-stamped series of CGM or BG data recorded for each person. Summary characteristics and group-level analyses are derived after the individual traces are processed to produce meaningful individual markers of average glycemia

and glucose variation. The analytical methodology is driven by the understanding that BG fluctuations are a continuous process in time, $BG(t)$. Each point of this process is characterized by its value (BG level) and by its rate/direction of BG change. A CGM presents the process $BG(t)$ as a discrete time series $\{BG(t_n), n = 1, 2, \dots\}$ that approximates $BG(t)$ in steps determined by the resolution of the particular device (e.g., a reading every 5 min).

With this in mind, we first review the concept of accuracy of CGM devices, which is broader than the concept of accuracy of self-monitored BG (SMBG) or other point measurements because CGM provide not only isolated readings, but also rate and direction of BG fluctuations, e.g., trends. Further, we discuss three types of statistical analyses suitable for the retrieval of CGM data: (1) average BG and deviations from normoglycemia, (2) variability and risk assessment, and (3) clinical events, such as post-meal glucose excursions and hypoglycemic episodes. Most risk and deviation measures are presented in both numerical and graphical forms, allowing both statistical comparisons and visual interpretation of the results. Finally, we review Control Variability-Grid Analysis

(CVGA), which follows the zone concept of Error Grid Analysis (EGA), to visualize the variability of CGM data at a group level from a glucose-control point of view.

Analyzing the Accuracy of CGM Data

Numerical accuracy

The accuracy of the data generated by various CGM systems has been described using both numerical and clinical statistical tools.¹⁻⁸ Generally speaking, the Food and Drug Administration requirements for the demonstration of numerical accuracy of CGM systems have been identical to those proscribed for the less complex self-BG monitors (SBGMs). They include the analysis of single reference-monitor glucose pairs and include mean and median relative absolute difference ($[(\text{Sensor} - \text{Reference})/\text{Reference}] \times 100\%$), correlation coefficients, and International Standardization Organization (ISO) criteria (sensor value within 15 mg/dL when reference BG ≤ 75 mg/dL, sensor value within $\pm 20\%$ when reference > 75 mg/dL). With the exception of ISO criteria, data pair accuracy is presented across the entire BG scale and not reported for the three clinically critical BG ranges (hypoglycemia, euglycemia, hyperglycemia).¹⁻³

These accuracy data might be considered complete if the CGM systems were merely interstitial glucose monitors and not "continuous" systems. "Continuous" implies a relationship between data pairs that cannot be assumed or approximated with the discrete unrelated BG values determined using SBGM. It is this continuous component that distinguishes CGM from the less complex SBGM, permits advanced decision-making by patients, and paves the way for the development of closed-loop (artificial pancreas) insulin delivery systems. Each BG value generated using a CGM is related in time and in direction to that of the previous BG value. For example, a CGM data stream of 87, 82, 78 mg/dL is not the same as a CGM data stream of 78, 82, 87 mg/dL even though the data pairs might satisfy all Food and Drug Administration-mandated accuracy standards. Thus a measure of accuracy of rate and direction of BG change needs to be a part of any accuracy analysis of CGM data. We have recently suggested the computation of "R deviation (RD)" as a metric of rate of change accuracy, where RD (in mg/dL/min) = (rate of change of reference - rate of change of CGM)/time interval.⁶ The mean RD is analogous to mean error in point accuracy.

Clinical accuracy

Food and Drug Administration criteria for SBGM approval also include a measure of clinical accuracy, EGA.⁹ EGA categorizes SBGM-reference data pairs in terms of the consequences of treatment decisions. Five zones of clinical accuracy are defined: Zone A, clinically accurate, SMBG within 20% of reference and/or SMBG reading < 70 mg/dL when reference is < 70 mg/dL; Zone B, benign errors, SMBG difference $> 20\%$ but error would not lead to either serious hypo or hyperglycemia; Zone C, overcorrection errors, SMBG above or below the target range of 70–180 mg/dL when reference is within target, and treatment would result in either hypo- or hyperglycemia; Zone D, failure to detect (hypo- or hyperglycemia) errors, SMBG values within target range when reference is either above or below target; and Zone E, erroneous treatment

errors, SMBG is either above or below target and reference is in the opposite extreme, resulting in insulin being given when BG is < 70 mg/dL or rapid-acting glucose being given when reference is > 180 mg/dL. EGA has been used by manufacturers to characterize the clinical accuracy of most SMBG systems. EGA also has been used by manufacturers of CGM systems to describe the clinical accuracy of their devices.¹⁻³ Such reports display a significant number of Zone D errors, most of which involve failures to detect BG < 70 mg/dL. Also, clinical accuracy (Zone A) has been similar to that reported years ago for visually interpreted Chemstrips BG (Boehringer Mannheim, Mannheim, Germany) stored in a dessicator vial for 5 days.¹⁰ The immediate conclusion is that CGM data are not sufficiently clinically accurate to permit safe treatment decisions. However, as noted above, the complete data set is not being analyzed when point accuracy alone is used.

Data generated with CGM are far richer than those generated by SBGM and include rate and direction of change. The original EGA was designed to evaluate point accuracy and cannot evaluate the rate and direction components of CGM data. Including these dimensions could significantly affect the clinical accuracy of the data sets. For instance, even when the CGM-reference data pair are identical values, if the direction of change is in error the treatment decision could result in serious hypo- or hyperglycemia. Likewise, the CGM-reference data pair could represent a failure to detect BG < 70 mg/dL (such as a CGM value of 84 mg/dL, reference value of 68 mg/dL), but if the rate of change was falling ≥ 4 mg/dL/min, a clinically correct treatment decision to prevent serious hypoglycemia could be made. Such possible scenarios stimulated the development of the Continuous Glucose-EGA (CG-EGA), which includes both point accuracy⁴ and a newly developed Rate Error Grid (Fig. 1).⁴ The Rate Error Grid categorizes rate and direction errors in zones similar to those for the original Point Error Grid. The Point Error Grid component of CG-EGA is the original EGA expanded for rapidly changing glucose values based on the rate and direction of change and the assumed lag time between BG and interstitial BG. In addition, accuracy with the CG-EGA is reported separately for the three critically important BG ranges: hypoglycemia, euglycemia, and hyperglycemia. CG-EGA has been used to evaluate the clinical accuracy of large data sets provided by several manufacturers and to compare the simultaneous clinical accuracy of different CGM systems during clamped euglycemia and hypoglycemia.^{4,5,7}

Statistical Tools for Interpreting CGM Data

Average glycemia and deviations from target

Numerical measures. The computation of mean glucose values from CGM data and/or BG data points is straightforward and is suggested as a descriptor of overall glycemic control. Computing of pre- and post-meal averages and their difference can serve as an indication of the overall effectiveness of pre-meal bolus timing and amount. Similarly, the percentages of time spent within, below, or above preset target limits would serve as indication of the general behavior of CGM fluctuations. The suggested limits are 70 and 180 mg/dL, which create three clinically different glycemic regions suggested by the Diabetes Control and Complications Trial¹¹ and commonly accepted bands: hypoglycemia (BG

FIG. 1. Rate Error Grid analysis that categorizes rate and direction sensor errors in zones similar to those for the original Clarke Error Grid⁴: Zone A, clinically accurate; Zone B, benign errors; Zone C, overcorrection errors; Zone D, failure to treat errors; and Zone E, erroneous treatment errors.

≤ 70 mg/dL),¹² target range (70 mg/dL $< BG \leq 180$ mg/dL), and hyperglycemia ($BG > 180$ mg/dL). Percentage of time within additional ranges can be computed as well to emphasize the frequency of extreme glucose excursions. For example, when it is important to distinguish between

postprandial and postabsorptive (fasting) conditions, a fasting target range of 70 – 140 mg/dL is suggested. Further, percentage of time < 50 mg/dL would quantify the frequency of significant hypoglycemia, whereas percentage of time > 300 mg/dL would quantify the frequency of significant hyperglycemia occurring during a clinical trial. Table 1 includes the numerical measures of average glycemia (Table 1A) and deviations from target (Table 1B). All these measures are computed per CGM trace per person, after which they can be used as a base for further group comparisons and other statistical analyses.

Graphs. While plotting the CGM trace observed during the experiment would represent the general pattern of a person's BG fluctuation, additional graphs are suggested to emphasize details of such a pattern corresponding to the numerical measures of the previous section. To illustrate the effect of treatment observed via CGM we use previously published 72-h glucose traces observed pre- and 4 weeks post-islet transplantation.¹³

Figure 2 presents the glucose traces [process $BG(t)$] pre- and post-transplantation with superimposed *aggregated glucose traces*. These traces are related to time spent below/within/above target range. The premise behind aggregation is as follows: frequently one is not particularly interested in the exact BG value because close values such as 150 and 156 mg/dL are clinically indistinguishable. It is, however, important whether and when BG crosses certain thresholds, e.g., 70 and 180 mg/dL as specified in the previous section. Thus, the entire process $BG(t)$ can be aggregated into a process described only by the crossings of the thresholds of hypoglycemia and hyperglycemia.

In Figure 2 the aggregated process is depicted by squares that are red for hypoglycemia, green for target range, and yellow for hyperglycemia. To reduce the influence of CGM

TABLE 1. NUMERICAL MEASURES OF SUMMARIZING CGM DATA

A: Average glycemia and deviations from target	
Mean BG	Computed from CGM or BG data for the entire test
Mean pre-meal BG	Mean BG restricted to time window 60–0 min pre-meals
Mean post-meal BG	Mean BG restricted to time window 60–120 min post-meals
B: Deviations from target	
% time spent within target range of 70 – 180 mg/dL, below 70 mg/dL, and above 180 mg/dL	For CGM, this generally equals percentage of readings within each of these ranges. For BG measurements that are not equally spaced in time we suggest calculating the percentage of time within each range via linear interpolation between consecutive glucose readings.
% time ≤ 50 mg/dL	Optional, to emphasize occurrence of extreme hypoglycemia
% time > 300 mg/dL	Optional, to emphasize occurrence of extreme hyperglycemia
C: Variability and risk assessment	
Interquartile range BGRI	
LBGI	Measure of variability suitable for non-symmetric distributions; $=LBGI + HBGI$, a measure of overall
HBGI	variability and risks of hypo- and hyperglycemia
SD of BG Rate of Change	Measure of the frequency and extent of low BG readings
D: Events and other clinical characteristics	Measure of the frequency and extent of high BG readings
Events of low BG < 70 mg/dL (or events of BGs < 50 mg/dL)	A measure of the stability of closed-loop control over time
Events of high BG > 180 mg/dL (or BGs > 300 mg/dL)

FIG. 2. Glucose traces (A) pre- and (B) post-transplantation with superimposed aggregated glucose traces, which are depicted by red squares for hypoglycemia, green for target range, and yellow for hyperglycemia. To reduce the influence of CGM errors, each square represents the average of 1 h of CGM data. Color images available online at www.liebertonline.com/dia

errors, each square represents the average of 1 h of CGM data. The aggregated process presents a clearer visual interpretation of the changes resulting from islet transplantation: post-treatment most of the BG fluctuations are within target, leading to a higher density of green squares. Possible versions of this plot include adding thresholds, such as 50 and 300 mg/dL, which would increase to five the levels of the aggregated process, and a higher resolution of the plot in the hypoglycemic range where one square of the aggregated process would be the average of $\frac{1}{2}$ h of data. Another representation of the distribution of glucose values with overlaid percentage of time spent in target/outside target is given by a density plot (Fig. 2). Table 2A includes a summary of the suggested graphs.

Variability and risk assessment

Numerical measures of glucose variability. Computing SD as a measure of glucose variability of CGM data is not recommended when analyzing BG data because the BG measurement scale is highly asymmetric, the hypoglycemic

range is numerically narrower than the hyperglycemic range, and the distribution of the glucose values of an individual is typically quite skewed.¹⁴ Therefore SD would be predominantly influenced by hyperglycemic excursions and would not be sensitive to hypoglycemia. It is also possible for confidence intervals based on SD to assume unrealistic negative values. Thus, standard measures such as the interquartile range would be more suitable for non-symmetric distributions. In addition, the BG risk index (BGRI) (defined below) can serve as a measure of overall glucose variability when focusing of the relationship between glucose variability and risks for hypo- and hyperglycemia. We have to emphasize that SD is very well suited to capture the variability of symmetric data, such as the variability of the BG rate of change (see Fig. 4). In other words, while BG data points typically have skewed distributions, the distribution of the change in BG is typically symmetric and suitable for SD analysis.

Numerical measures of risk. In order to capture both glucose variability and its associated risks for hypo- and

TABLE 2. GRAPHS VISUALIZING CGM DATA

A: Average glycemia and deviations from target Glucose trace (Fig. 2) Aggregated glucose trace (Fig. 3)	Traditional plot of frequently sample glucose data Corresponds to time spent below/within/above a preset target range; visualizes the crossing of glycemic thresholds
B: Variability and risk assessment Risk trace (Fig. 3)	Corresponds to LBGI, HBGI, and BGRI; designed to equalize the size of glucose deviations towards hypo- and hyperglycemia, emphasize large glucose excursions, and suppress fluctuation within target range, thereby highlighting essential variance
Histogram of BG Rate of Change (Fig. 4)	Represents the spread and range of glucose transitions; related to system stability; corresponds to SD of BG Rate of Change
Poincaré plot (Fig. 5)	The spread of the data indicates system (patient) stability—more widespread data points are associated with unstable diabetes and rapid glucose fluctuations
C: Event-based clinical characteristics CVGA (Fig. 6)	Represents the effectiveness of glycemic control at a group level; corresponds to event-based characteristics

hyperglycemia, we suggest variability and risk measures, as well as risk plots that are based on a symmetrization of the BG measurement scale.¹⁴ These symmetrization formulas are data independent and have been used successfully in numerous studies.^{13–17} In brief, for any BG reading we first compute:

$$f(BG) = 1.509 \times [(\ln(BG))^{1.084} - 5.381] \quad \text{if } BG \text{ is measured in mg/dL, or}$$

$$f(BG) = 1.509 \times [(\ln(18 \times BG))^{1.084} - 5.381] \quad \text{if } BG \text{ is measured in mmol/L}$$

Then we compute the BG risk function using the formula $r(BG) = 10 \times f(BG)^2$ and separate its left and right branches corresponding to low “*rl*” and high “*rh*” BG as follows:

$$rl(BG) = r(BG) \quad \text{if } f(BG) < 0 \text{ and } 0 \text{ otherwise}$$

$$rh(BG) = r(BG) \quad \text{if } f(BG) > 0 \text{ and } 0 \text{ otherwise}$$

Given a series of CGM readings $BG_1, BG_2, \dots, BG_n$, we compute the Low and High BG indices (LBGI and HBGI, respectively) as the average of $rl(BG)$ and $rh(BG)$, respectively^{13,15}:

$$LBGI = \frac{1}{n} \sum_{i=1}^n rl(BG_i) \quad \text{and} \quad HBGI = \frac{1}{n} \sum_{i=1}^n rh(BG_i)$$

The BGRI is then defined as $BGRI = LBGI + HBGI$.

In essence, the LBGI and the HBGI split the overall glucose variation into two independent sections related to excursions into hypo- and hyperglycemia, and at the same time equalize the amplitude of these excursions with respect to the risk they carry. For example, a BG transition from 180 to 250 mg/dL would appear threefold larger than a transition from 70 to 50 mg/dL, whereas if converted into risk, these fluctuations would appear equal. Using the LBGI, HBGI, and their sum BGRI complements the use of thresholds described above by adding information about the *extent of BG fluctuations*. A simple example would clarify this point: assume two sets of BG readings, (110,65) and (110,40) mg/dL. In both cases we have 50% of readings below the threshold of 70 mg/dL; thus

the percentage of readings below target is 50% in both cases. However, the two scenarios are hardly equivalent in terms of risk for hypoglycemia, which is clearly depicted by the difference in their respective LBGI values: 5.1 and 18.2. A detailed description of the theoretical background and the practical application of the risk indices can be found elsewhere.^{13,15–17} The LBGI and the HBGI have been linked to the frequency and extent of hypo- and hyperglycemic episodes, respectively. In repeated studies^{15–17} it has been established that four risk categories of the LBGI can be identified: minimal risk for hypoglycemia, $LBGI \leq 1.1$; low risk, $1.1 < LBGI \leq 2.5$; moderate risk, $2.5 < LBGI \leq 5$; and high risk, $LBGI > 5$.¹⁷ Similarly, two cutoff points—4.5 and 9—have been identified for the HBGI separating low, moderate, and high risk for hyperglycemia.¹⁵ It has been shown that this categorization is particularly powerful for identifying people at risk for hypoglycemia—subjects at minimal risk experience prospectively zero severe hypoglycemic episodes and zero extreme low BG readings (below 40 mg/dL) during a 3-month follow-up, whereas subjects in the high-risk category experience over five such episodes.¹⁷

Numerical measures of patient BG stability. Analysis of BG rate of change (measured in mg/dL/min) is suggested as a way to evaluate the dynamics of BG fluctuations on the time scale of minutes. In mathematical terms, this is an evaluation of the “local” properties of the system as opposed to “global” properties discussed above. Being the focus of differential calculus, local functional properties are assessed at a neighborhood of any point in time t_0 by the value $BG(t_0)$ and the derivatives of $BG(t)$ at t_0 . The *BG Rate of Change* at t_i is computed as the ratio $[BG(t_i) - BG(t_{i-1})]/(t_i - t_{i-1})$, where $BG(t_i)$ and $BG(t_{i-1})$ are CGM or reference BG readings taken at times t_i and t_{i-1} that are close in time. Recent investigations of the frequency of glucose fluctuations show that optimal evaluation of the BG Rate of Change would be achieved over time periods of 15 min,^{18,19} e.g., $\Delta t = t_i - t_{i-1} = 15$. For data points equally spaced in time this computation provides an estimate of the derivative (slope) of $BG(t)$. A larger variation of the BG Rate of Change indicates rapid and more pronounced BG fluctuations and therefore a less stable system. Thus, we use the SD of the BG Rate of Change as a measure of stability of

FIG. 3. Risk traces (A) pre- and (B) post-islet transplantation determined by 72 h of continuous glucose monitoring. Color images available online at www.liebertonline.com/dia.

glucose fluctuation. Two points are worth noting: (1) as opposed to the distribution of BG levels, the distribution of the BG Rate of Change is *symmetric* and therefore using SD is statistically accurate,²⁰ and (2) the SD of BG Rate of Change is similar to a previously introduced measure of BG stability computed from CGM data known as CONGA—CONGA (n)/ n would be exactly the SD of the BG rate of change between two points that are n h apart.²⁰ Table 1C summarizes the suggested measures of glucose variability, system stability, and associated risks.

Graphs. Figure 3 presents 72-h traces of risk of BG fluctuation corresponding to the glucose traces of Figure 2 at baseline and post-islet transplantation (A and B, respectively). Each figure includes the fluctuations of the LBGI (lower half of each panel) and HBGI (upper half of each panel), with both indices computed from 1-h blocks. The magnitude of these fluctuations decreases as a result of treatment. The average LBGI was 6.72 at baseline and 2.90 post-transplantation. Similarly, the HBGI was reduced from 5.53 at baseline to 1.73 after islet transplantation. The advantages of risk plot include: (1) the variance carried by hypo- and hyperglycemic readings is equalized; (2) excursions into extreme hypo- and hyperglycemia get progressively increasing risk values; and (3) the variance within the safe euglycemic range is attenuated,

which reduces noise during data analysis. In essence, Figure 3 links better glycemic control to a narrower pattern of risk fluctuations. Because the LBGI, HBGI, and the combined BGRI can theoretically range from 0 to 100, their values can be interpreted as percentages of maximum possible risk.

Figure 4 presents histograms of the distribution of the BG Rate of Change over 15 min, computed from the Medtronic MiniMed (Northridge, CA) CGMS[®] data of the transplantation case shown in Figure 2. It is apparent that the baseline distribution is more widespread than the distribution post-transplantation. Numerically, this effect is reflected by 19.3% of BG rates outside of the $[-2, 2]$ mg/dL/min range in Figure 4A versus only 0.6% BG rates outside that range in Figure 4B. Thus, pretransplantation the patient experienced rapid BG fluctuations, whereas post-transplantation the rate of fluctuations was dramatically reduced. This effect is also captured by the SD of the BG Rate of Change, which is reduced from 1.58 to 0.69 mg/dL/min as a result of treatment.

Finally, another look at system (patient's BG) stability is provided by the Poincaré plot (lag plot) that is used in physics to visualize the dynamic behavior of the investigated system²¹: a smaller, more concentrated plot indicates system (patient) stability, whereas a more scattered Poincaré plot indicates system (patient) irregularity, reflecting in our case poorer glucose control and rapid glucose excursions. Each

FIG. 4. Histograms of the BG Rate of Change (A) pre- and (B) post-islet transplantation.

point of the plot has coordinates $BG(t_{i-1})$ on the x -axis and $BG(t_i)$ on the y -axis. Thus, the difference ($y-x$) coordinates of each data point represents the BG Rate of Change occurring between times t_{i-1} and t_i . Figure 5 presents Poincaré plots of CGM data at baseline and post-islet transplantation. The spread of the data is substantially larger before treatment compared with post-treatment. The principal axes of the Poincaré plot can be used as numerical metrics of system (patient) stability. Because at this time there are no normative data available on what would be a “normal” data spread, the

Poincaré plot is suggested for visualizing a treatment effect aiming stabilization of a patient’s BG fluctuations, which is not readily visible from traces. Table 2B includes a summary of the suggested graphs.

Events and other clinical characteristics

Metrics. CGM data can be used to register the occurrence and the timing of clinically significant events, such as hypoglycemic episodes and events of postprandial hyperglycemia.

FIG. 5. Poincaré plot of BG fluctuations (A) pre- and (B) post-islet transplantation. Color images available online at www.liebertonline.com/dia.

FIG. 6. Variability-grid analysis of patients prone to overcorrecting (A) hypoglycemia and (B) hyperglycemia.

While there is ongoing discussion whether two consecutive low BG events that are close in time (e.g., 30 min apart) should be considered a single or two separate events, it is suggested that counts of events per day are reported. However, visual inspection of the glucose trace should be employed to see whether discrete events of BG below or above certain threshold can be combined into single event of hypo- or hyperglycemia (see Table 1D).

To visualize the overall glycemic control, in particular glucose extremes, for a group of patients we have introduced CVGA,²² which is built on a minimum/maximum plot of glucose values with ideas similar to the ideas of the original Clarke EGA used for evaluation of the accuracy of self-monitoring⁹ or CGM devices.⁴ The CVGA is computed as follows: for each person a point is plotted with x -coordinate the minimum BG and y -coordinate the maximum BG for an observation period. To reject sensor errors, the minimum BG is set at the 2.5th percentile, and the maximum BG is set at the 97.5th percentile of the BG distribution (e.g., the y - x coordinate difference corresponds to the 95% spread of the observed BG distribution). The suggested observation period is 24 h (e.g., in a 3-day study each person would get three data points); however, modifications of the plot are possible to emphasize pre-to-postprandial glucose excursions or nocturnal control, which would limit the observation period to times around meals or during the night. The plot is then split into zones defined by their x - and y -coordinate ranges as follows (see Fig. 6 for zone definition):

A-zone, Accurate control with x -range 110–90 mg/dL and y -range 110–180 mg/dL

B-zone, Benign control deviations with x = 90–70 mg/dL and y = 180–300 mg/dL

Lower B, Benign deviations into hypoglycemia: x = 90–70 mg/dL, y = 110–180 mg/dL

Upper B, Benign deviations into hyperglycemia: x = 110–90 mg/dL, y = 180–300 mg/dL

Lower C, Over-Correction of hyperglycemia: x < 70 mg/dL, y = 110–180 mg/dL

Upper C, Over-Correction of hypoglycemia: x = 110–90 mg/dL, y > 300 mg/dL

Lower D, Failure to Deal with hypoglycemia: x < 70 mg/dL, y = 180–300 mg/dL

Upper D, Failure to Deal with hyperglycemia: x = 90–70 mg/dL, y > 300 mg/dL

E-zone, Erroneous control: x < 70 mg/dL and y > 300 mg/dL

Points exceeding the limits of the plot are plotted on the outer border. A reading in the A-zone signifies a control period during which glucose was kept within the range of 90–180 mg/dL, whereas a reading in the E-zone indicates that both hypoglycemia < 70 mg/dL and hyperglycemia > 300 mg/dL occurred within the same observation period.

As an example, Figure 6A presents a computer simulation of the CVGA of a group of patients whose control tends to overcorrect hypoglycemia, while Figure 6B presents patients who tend to overcorrect hyperglycemia. Numerical characteristics representing the CVGA are the percentages of points within each zone, typically grouped as A-zone, A + B-zones, and C + D + E-zones. For example, in Figure 6A we have 9% A-zone, 58% A + B-zone, and 42% control errors. Thus, the CVGA is a display of event-based clinical characteristics of the control algorithm. For these simulation experiments we used a previously presented computer simulation environment capable of approximating glucose patterns in 300 patients with type 1 diabetes mellitus.²³

Conclusions

The intent of this article is to present a set of mathematically rigorous methods that provide statistical and visual interpretation of frequently sampled BG data series that are typically recorded by contemporary CGMs. The reason for introducing new methods and opting for non-standard analyses is simple: CGM data are complex sets of data points that are ordered in time and dependent on each other when the time interval of sampling is relatively short (e.g., minutes). Thus, standard statistics that rely on independence of the observations for practically any conclusion may produce biased results. Two principal approaches are discussed: methods evaluating the accuracy of CGMs and methods analyzing and visualizing CGM data series.

In terms of accuracy, we suggest taking a 2×2 approach: Numerical-Clinical×Point-Rate accuracy. In other words, we suggest looking at both traditional numerical metrics, such as absolute deviation, and clinical metrics, such as EGA,⁴ and splitting each of these categories into point and rate (trend) accuracy estimates. The latter is important as CGM data represent time series, and the information of where the CGM trace might be going is almost equally important as the information where the trace is now. If a CGM has high rate (trend) accuracy, a number of treatment decisions become possible. For example, the device could warn for upcoming hypoglycemia, predict glucose deviations, or be used for closed-loop control (artificial pancreas).

In terms of data analysis approaches, we discuss risk and variability analysis methods and present several plots representing characteristics of CGM data that are not readily apparent by traditional statistical graphing. For example, the stability of a person's BG fluctuations can be depicted by a Poincaré plot of glucose dynamics, and the degree of variability in a group of patients can be visualized by the CVGA. These two plots can be used to judge the effectiveness of treatment aiming stabilization of BG fluctuations for an individual or for a group of patients, respectively.

We would therefore encourage investigators and clinicians to use the rich information contained in CGM data to guide their research and to provide feedback and instruction to their patients using CGM systems. As the accuracy of these systems improve, it is anticipated that their availability and use in clinical practice will increase and that they will stimulate new benchmarks and guideposts for the management of glycemia in persons with diabetes. New developments in the design and testing of closed loop systems for controlling glucose levels in type 1 diabetes mellitus are but one example of this potential.

The adoption of these analytical methods would be facilitated if CGM manufacturers implement the numerical and graphical displays presented in this paper in their CGM data retrieval software. We believe that such displays would provide valuable information to physician and patients in a condensed, easy-to-interpret format—information that otherwise may remain lost in the complexity of the CGM data stream.

Acknowledgments

The development of the presented metrics was supported by grant RO1 DK 51562 from the National Institutes of Health and by the JDRF Artificial Pancreas Consortium.

Author Disclosure Statement

W.C. and B.K. have received research grant support in the past from Abbott Diabetes Care, Alameda, CA, and are currently receiving study material support from Abbott Diabetes Care. W.C. is a member of the Speaker's Bureau for Smiths Medical. B.K. has received grants and material support from Lifescan, Milpitas, CA.

References

1. Food and Drug Administration: Summary of Safety and Effectiveness Data—Medtronic Guardian RT. Available online at: www.fda.gov/cdrh/PDF/p980022s01.pdf (accessed July 2005).
2. Food and Drug Administration: Summary of Safety and Effectiveness Data—STS-7 Continuous Glucose Monitoring System. Available online at: www.fda.gov/cdrh/pdf5/p050012s001b.pdf (accessed May 2007).
3. Food and Drug Administration: Summary of Safety and Effectiveness Data—FreeStyle Navigator Continuous Glucose Monitoring System. Available online at: www.fda.gov/cdrh/pdf5/p050020b.pdf (accessed March 2008).
4. Kovatchev B, Gonder-Frederick L, Cox D, Clarke W: Evaluating the accuracy of continuous glucose monitoring sensors. *Diabetes Care* 2004;27:1922–1928.
5. Clarke W, Anderson S, Farhy L, Breton M, Gonder-Frederick L, Cox D, Kovatchev B: Evaluating the clinical accuracy of two continuous glucose sensors using continuous glucose-error grid analysis. *Diabetes Care* 2005;28:2412–2417.
6. Clarke W, Kovatchev B: Continuous glucose sensors: continuing questions about clinical accuracy. *J Diabetes Sci Technol* 2007;1:669–675.
7. Kovatchev B, Anderson S, Heinemann L, Clarke W: Comparison of the numerical and clinical accuracy of four continuous glucose monitors. *Diabetes Care* 2008;31:1160–1164.
8. Clarke W, Anderson S, Kovatchev B: Evaluating clinical accuracy of continuous glucose monitoring systems: continuous glucose-error grid analysis (CG-EGA). *Curr Diabetes Rev* 2008;4:193–199.
9. Clarke W, Cox D, Gonder-Frederick L, Carter W, Pohl S: Evaluating the clinical accuracy of self-blood glucose monitoring systems. *Diabetes Care* 1987;10:622–628.
10. Cox D, Herrman J, Snyder A, Gonder-Frederick L, Reschke J, Clarke W: Stability of reacted Chemstrip bG. *Diabetes Care* 1988;11:288–291.
11. The effect of intensive treatment of diabetes on the development and progression of long-term complications of insulin-dependent diabetes mellitus. *Diabetes Control and Complications Trial Research Group. N Engl J Med* 1993; 329:978–986.
12. American Diabetes Association Workgroup on Hypoglycemia: Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005;28:1245–1249.
13. Kovatchev BP, Clarke WL, Breton M, Brayman K, McCall A: Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. *Diabetes Technol Ther* 2005;7:849–862.
14. Kovatchev B, Cox D, Gonder-Frederick L, Clarke W: Symmetrization of the blood glucose measurement scale and its applications. *Diabetes Care* 1997;20:1655–1658.
15. Kovatchev BP, Straume M, Cox DJ, Farhi LS: Risk analysis of blood glucose data: a quantitative approach to optimizing

- the control of insulin dependent diabetes. *J Theor Med* 2001; 3:1–10.
16. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke WL: Methods for quantifying self-monitoring blood glucose profiles exemplified by an examination of blood glucose patterns in patients with type 1 and type 2 diabetes. *Diabetes Technol Ther* 2002;4:295–303.
 17. Kovatchev BP, Cox DJ, Kumar A, Gonder-Frederick LA, Clarke WL: Algorithmic evaluation of metabolic control and risk of severe hypoglycemia in type 1 and type 2 diabetes using self-monitoring blood glucose data. *Diabetes Technol Ther* 2003;5:817–828.
 18. Miller M, Strange P: Use of Fourier models for analysis and interpretation of continuous glucose monitoring glucose profiles. *J Diabetes Sci Technol* 2007;1:630–638.
 19. Breton MD, Shields DP, Kovatchev BP: Optimum subcutaneous glucose sampling and Fourier analysis of continuous glucose monitors. *J Diabetes Sci Technol* 2008;2:495–500.
 20. McDonnell CM, Donath SM, Vidmar SI, Werther GA, Cameron FJ: A novel approach to continuous glucose analysis utilizing glycemic variation. *Diabetes Technol Ther* 2005;7: 253–263.
 21. Brennan M, Palaniswami M, Kamen P: Do existing measures of Poincare plot geometry reflect nonlinear features of heart rate variability? *IEEE Trans Biomed Eng* 2001;48:1342–1347.
 22. Magni L, Raimondo F, Dalla Man C, Breton MD, Patek S, De Nicolao G, Cobelli C, Kovatchev BP: Evaluating the efficacy of closed-loop glucose regulation via control-variability grid analysis. *J Diabetes Sci Technol* 2008;2:630–635.
 23. Kovatchev BP, Breton MD, Dalla Man C, Cobelli C: In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. *J Diabetes Sci Technol* 2009;3:44–55.

Address reprint requests to:

William L. Clarke, M.D.

Box 800386

Department of Pediatrics

University of Virginia Health Sciences Center

Charlottesville, VA 22908

E-mail: wlc@virginia.edu