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Numerical Simulation of the Effect of Rate of Change of Glucose on Measurement Error of Continuous Glucose Monitors

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Abstract

Background:

A 5-day in-patient study designed to assess the accuracy of the FreeStyle Navigator® Continuous Glucose Monitoring System revealed that the level of accuracy of the continuous sensor measurements was dependent on the rate of glucose change. When the absolute rate of change was less than 1 mg•dl^{-1}•min^{-1} (75% of the time), the median absolute relative difference (ARD) was 8.5%, with 85% of all points falling within the A zone of the Clarke error grid. When the absolute rate of change was greater than 2 mg•dl^{-1}•min^{-1} (8% of the time), the median ARD was 17.5%, with 59% of all points falling within the Clarke A zone.

Method:

Numerical simulations were performed to investigate effects of the rate of change of glucose on sensor measurement error. This approach enabled physiologically relevant distributions of glucose values to be reordered to explore the effect of different glucose rate-of-change distributions on apparent sensor accuracy.

Results:

The physiological lag between blood and interstitial fluid glucose levels is sufficient to account for the observed difference in sensor accuracy between periods of stable glucose and periods of rapidly changing glucose.

Conclusions:

The role of physiological lag on the apparent decrease in sensor accuracy at high glucose rates of change has implications for clinical study design, regulatory review of continuous glucose sensors, and development of performance standards for this new technology. This work demonstrates the difficulty in comparing accuracy measures between different clinical studies and highlights the need for studies to include both relevant glucose distributions and relevant glucose rate-of-change distributions.

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Abbreviations: (ARD) absolute relative difference, (CGMetric) Continuous Glucose Metric, (CV) coefficient of variation, (FDA) Food and Drug Administration, (ISF) interstitial fluid

Keywords: continuous glucose monitoring system, glucose, glucose monitoring, glucose sensors, Navigator

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Introduction

Recent studies involving the use of continuous glucose monitoring have highlighted the limitations of current diabetes therapy involving episodic self-monitoring of blood glucose. A 3-day study with 56 children with type 1 diabetes using a continuous glucose monitoring system (Medtronic MiniMed, Northridge, CA) in which glucose data were not displayed to the patients found 90% of postprandial glucose values in the hyperglycemic range (>180 mg/dl) with 50% markedly hyperglycemic (>300 mg/dl).[1] A 21-day study with 101 adults with type 1 (n = 60) and type 2 (n = 41) diabetes using the FreeStyle Navigator® Continuous Glucose Monitoring System (Abbott Diabetes Care, Alameda, CA) in which glucose data were also not displayed to the patients found subjects were hypoglycemic (<70 mg/dl) for 1.9 hours per day and hyperglycemic (>180 mg/dl) for 6.9 hours per day despite frequent blood glucose testing, averaging 7.9 tests per day.[2]

Continuous glucose monitoring is expected to assist patients with diabetes in achieving safer tight glycemic control more effectively.[3–5] Historically, patients on intensive insulin therapy have had a markedly higher incidence of hypoglycemia.[6] Accordingly, both the occurrence and the fear of hypoglycemia have been identified as primary barriers to effective glycemic control.[7] Patients using continuous glucose monitoring devices may be able to set more aggressive glycemic targets and therefore treat hyperglycemia more aggressively without incurring an increase in the incidence of hypoglycemia. Continuous glucose monitoring systems may further enable patients to reduce glycemic fluctuations, which have received increased attention for their role in the development of diabetic complications.[8,9] Finally, accurate and reliable continuous glucose monitors are essential elements in the development of any future artificial pancreas devices incorporating automated insulin infusion.[10,11]

The utility of continuous glucose monitoring devices will largely be determined by the accuracy of the information that they can provide to both patients and their health-care providers. A 5-day in-patient study involving 58 subjects with type 1 diabetes was conducted to assess the accuracy of the FreeStyle Navigator system. Readings from the FreeStyle Navigator system were compared with frequent venous samples analyzed with an accepted clinical laboratory instrument. From all subjects, a total of 20,362 paired points between the FreeStyle Navigator system and the laboratory reference were collected during 50 hours of sampling scheduled throughout the 5 days of sensor wear. At the time of the study, the FreeStyle Navigator system was an investigational device under review by the U.S. Food and Drug Administration (FDA).

In this study, the median absolute relative difference (ARD) of the FreeStyle Navigator system was found to be 9.3%, with 82% of the paired points falling within the clinically accurate A zone of the Clarke error grid.[12] The study also revealed that the level of accuracy of the continuous sensor measurements was dependent on the rate of glucose change.

When glucose values were relatively stable, meaning that the absolute rate of change was less than 1 mg•dl^{-1}•min^{-1} (75% of the time), the median ARD was 8.5%, with 85% of all points falling within the Clarke A zone. During the course of the 50 hours of frequent reference venous glucose sampling, study subjects were administered both insulin and glucose challenges in order to obtain periods of rapidly rising and rapidly falling glucose. When the absolute rate of blood glucose change was greater than 2 mg•dl^{-1}•min^{-1} (6.6% of the time), the median ARD was 17.5%, with 59% of all points falling within the Clarke A zone. The frequency of these high rates of glucose change is consistent with what has been observed in simulated home-use studies.[13,14] These results are summarized in **Table 1**.

Table 1.
Results from 5-Day In-Patient Study Using the Freestyle Navigator Continuous Glucose Monitoring System Demonstrate That Accuracy, as Measured by Standard Metrics, Is Strongly Dependent on Glucose Rate of Change

Rate of change (mg•dl^{-1}•min^{-1})	% of data	Clarke error grid zone					Median ARD (%)
		A	B	C	D	E	
<-2	3.1	54.6%	42.3%	1.3%	1.8%	0.0%	17.4
-2 to -1	8.8	71.7%	26.2%	0.3%	1.8%	0.0%	11.8
-1 to 1	74.7	84.9%	13.5%	0.0%	1.5%	0.0%	8.5
1 to 2	10.0	79.8%	18.9%	0.0%	1.3%	0.0%	11.0
>2	3.5	63.5%	34.7%	0.0%	1.7%	0.0%	16.9

An analysis was undertaken to elucidate the relationship between the observed accuracy and the glucose rate of change and to explore the role of the lag between blood and interstitial fluid (ISF) glucose measurements on this dynamic.

This lag is generally reported to range between 0 and 15 minutes and is observed most readily during periods of rapidly changing blood glucose,[15] which can be understood in terms of dynamic delay and dynamic error. Here, dynamic delay refers to the temporal delay for a transient change in blood glucose to be reflected in ISF glucose and is associated with the properties of mass transfer between compartments. Alternately, dynamic error is the difference between the glucose level in the blood and in the ISF and is the product of the dynamic delay and the rate of change in glucose. As such, the dynamic error, which is the observable manifestation of lag and which is reflected in standard accuracy metrics, is most pronounced during periods of rapidly changing glucose.[16]

Methods

A numerical simulation program, Continuous Glucose Metric (CGMetric) (Abbott Diabetes Care, Alameda, CA), was used to investigate sources of error in continuous glucose monitoring, focusing on the relationship between the rate of change of glucose and measures of sensor accuracy.

These sources of error have been well enumerated and include both instrumental and physiological sources. Instrumental sources may include such things as bias, drift, noise, and sensor response time.[17] Physiological sources are associated primarily with the compartment in which continuous glucose measurements are made. Whereas current standards of treatment for the management of diabetes involve self-monitoring of capillary blood glucose, the present generation of continuous glucose monitoring systems (those systems approved for use as well as those currently under review by the FDA) involves subcutaneous sensors that measure glucose in the ISF and which are calibrated to reflect blood glucose levels. As such, physiological sources of error may include the concentration gradient between capillary blood glucose and ISF glucose levels, as well as any lag that exists as a consequence of the dynamic relationship between the two compartments.[18]

CGMetric was designed to gain an understanding of the maximum accuracy (or the minimum error) that could be expected for a given data set (or, alternatively, a given clinical study design) when comparing continuous glucose monitoring results to blood glucose reference values. The program allows real or simulated continuous glucose data to be analyzed using standard accuracy metrics with respect to appropriate pseudo-reference data. Continuous glucose data are imported into the simulation environment, and values at regular intervals (e.g., 15 or 30 minutes) are selected to serve as pseudo-reference data. Imported continuous glucose data can then be perturbed by introducing lag, drift, bias, and noise. Pseudo-reference data are left unperturbed. Perturbed continuous data can then be analyzed with respect to pseudo-reference data, and standard measures of accuracy can be calculated to allow the sources of error in continuous glucose monitoring to be studied independently or in conjunction with one another.

The basic functionalities of the CGMetric program were validated using simple analytical functions as the imported continuous glucose data sets. These data sets were perturbed as described earlier, and the reported accuracy measures were compared with those calculated independently.

The CGMetric program also allows for imported continuous glucose data sets to be preconditioned prior to perturbation. Preconditioning may include the rearrangement of continuous glucose data to systematically alter the glucose rate-of-change distribution. For example, if glucose values in the imported data set are ordered from lowest to highest, this creates a glucose rate-of-change distribution that is skewed toward lower rates of change. Alternatively, glucose values may be systematically rearranged such that a higher frequency of large glucose rates of change can be observed. For illustration, glucose values can be rearranged by dealing out the values such that the lowest value is first, the second lowest is last, the third lowest is second, the fourth lowest is second to last, and so on. This creates a data set with a characteristic frequency equal to half that of the simply ordered data set. This procedure may be repeated, each time shuffling and redealing out the same glucose values to achieve increasing rates of change. In this way, the distribution of glucose values is kept constant while the distribution of the rates of change may be rearranged such that the effect of different glucose rate-of-change distributions on apparent sensor accuracy can be explored.

The Wired Enzyme™ sensor chemistry used by the FreeStyle Navigator Continuous Glucose Monitoring System minimizes the instrumental error associated with that device.[19] The sensor is largely unaffected by bias and

drift, as demonstrated by the reported agreement between FreeStyle Navigator system glucose measurements and those obtained from a clinical laboratory reference instrument and from the similar performance observed on the first and fifth days of wear (12.6% mean ARD on day 1 as compared to 13.0% mean ARD on day 5) despite only four required calibrations over the 5 days of wear (including none during the final 48 hours). Accordingly, bias and drift were not applied to the data sets in the simulations reported here.

Comparison of the accuracy of FreeStyle Navigator sensors worn on the arm and abdomen simultaneously showed no clinical or statistically significant difference. Matched sensors had a coefficient of variation (CV) of 10%, consistent with a random noise level, including both sensor noise and any error imparted during calibration, of approximately 20%.[12]

A temporal delay in continuous glucose monitoring is studied most appropriately using a diffusion model that addresses the properties of mass transfer between blood and ISF compartments.[20] However, simplification of a fixed temporal offset is often referenced in the literature. The CGMetric program was used to model the effects of lag using both a fixed temporal offset of 12 minutes, consistent with results of an analysis of time-shifted FreeStyle Navigator data from the 5-day in-patient study, which found that the mean ARD could be minimized if a 12.6-minute offset were applied,[12] and a two-compartment diffusion model with a time constant, τ, of 9 minutes.[21] Numerical simulations revealed only minor differences between the two methods over physiologically relevant rates of glucose change. For simplicity, all data reported here were obtained using a fixed temporal offset of 12 minutes unless otherwise noted.

Data used in the following analyses were obtained as part of a clinical study conducted at Diablo Clinical Research (Walnut Creek, CA). The protocol was approved by an institutional review board and the subjects gave informed consent for their participation.

Results

A typical 24-hour glucose profile obtained from a subject with type 1 diabetes is used as seed data for the simulations discussed later. This glucose profile is shown in **Figure 1** along with graphs that identify distributions of the glucose values and the glucose rates of change.

During the period of observation the subject's blood glucose, as measured once per minute by the FreeStyle Navigator system, was less than 80 mg/dl 24% of the time, between 80 and 200 mg/dl 65% of the time, and above 200 mg/dl 9% of the time. The glucose values ranged from 43 to 353 mg/dl. The glucose rate of change was calculated using data obtained from the FreeStyle Navigator system after the application of a low-pass filter which retained the physiological fluctuations in the subject's blood glucose while significantly reducing the random error associated with the derivative used to calculate the glucose rate of change. This is demonstrated in **Figure 1** by the agreement of the smoothed data with the original dataset. The low-pass filter employed used a Fourier transform (Numerical Recipes, v. 2.11) with a look back of 30 minutes.

During this 24-hour period, the subject's glucose was relatively stable, changing at a rate between -1 and 1 $mg \cdot dl^{-1} \cdot min^{-1}$ 63% of the time; moderately unstable, with an absolute rate of change between 1 and 2 $mg \cdot dl^{-1} \cdot min^{-1}$ 25% of the time; and highly unstable, with an absolute rate of change greater than 2 $mg \cdot dl^{-1} \cdot min^{-1}$ 12% of the time.

In the first example presented, the imported continuous glucose data set was analyzed with the temporal integrity intact (i.e., preserving both glucose distribution and glucose rate-of-change distribution). Pseudo-reference data were selected from the imported data set at 15-minute intervals. The imported data set was subjected to a perturbation involving the application of 20% random noise and a temporal offset of 12 minutes. (In all cases where the signal perturbation included random noise, Visual Basic "Randomize" and "Rnd" functions were used to generate pseudo-random values based on the indicated percentage of imported continuous glucose data.) Perturbed data were then compared to pseudo-reference data and standard accuracy metrics were calculated. This procedure was performed 10 times on the original imported data set such that statistical measures of accuracy averaged over the ensemble results could be reported. Results of the analysis of perturbed data, shown in **Figure 2**, reveal a median ARD of 12.0% (range 10.4–13.2%) with 80% (range 75–85%) of all points falling within the Clarke A zone, consistent with the level of accuracy observed for the FreeStyle Navigator system in the 5-day in-patient study.

In the next example offered, the imported data set was preconditioned prior to perturbation and the selection of pseudo-reference values was such that the distribution of glucose values could be kept constant while the distribution of the glucose rate-of-change could be varied widely, as shown in **Figure 3**. Glucose rate-of-change distributions with between 1 and 38% of all points with

an absolute rate of change greater than 2 mg•dl^{-1}•min^{-1} were utilized. The identical perturbation as used in the previous example, involving the addition of 20% random noise and a temporal offset of 12 minutes, was applied to these preconditioned data sets and statistical measures of accuracy were calculated. Both the median ARD and the percentage of paired points falling in the Clarke A zone were observed to depend strongly on the glucose rate-of-change distribution. With decreasing glucose stability (as quantified by an increasing percentage of glucose values with an absolute rate of change greater than 2 mg•dl^{-1}•min^{-1}), the median ARD was observed to rise and the percentage of paired points falling in the Clarke A zone was observed to fall (**Figure 4**).

Discussion

The approach presented here provides unique insight into the relationship among the rate of change of glucose, the physiological lag between blood glucose and interstitial fluid glucose, and statistical measures of sensor accuracy. The model developed for analyzing the performance of the FreeStyle Navigator Continuous Glucose Monitoring System—based on only the measured system characteristics of a random noise level of 20% and a temporal lag of 12 minutes—was able to simulate the level of accuracy observed in the aggregate statistical results obtained from the 5-day in-patient study. In addition, the aforementioned analysis was able to

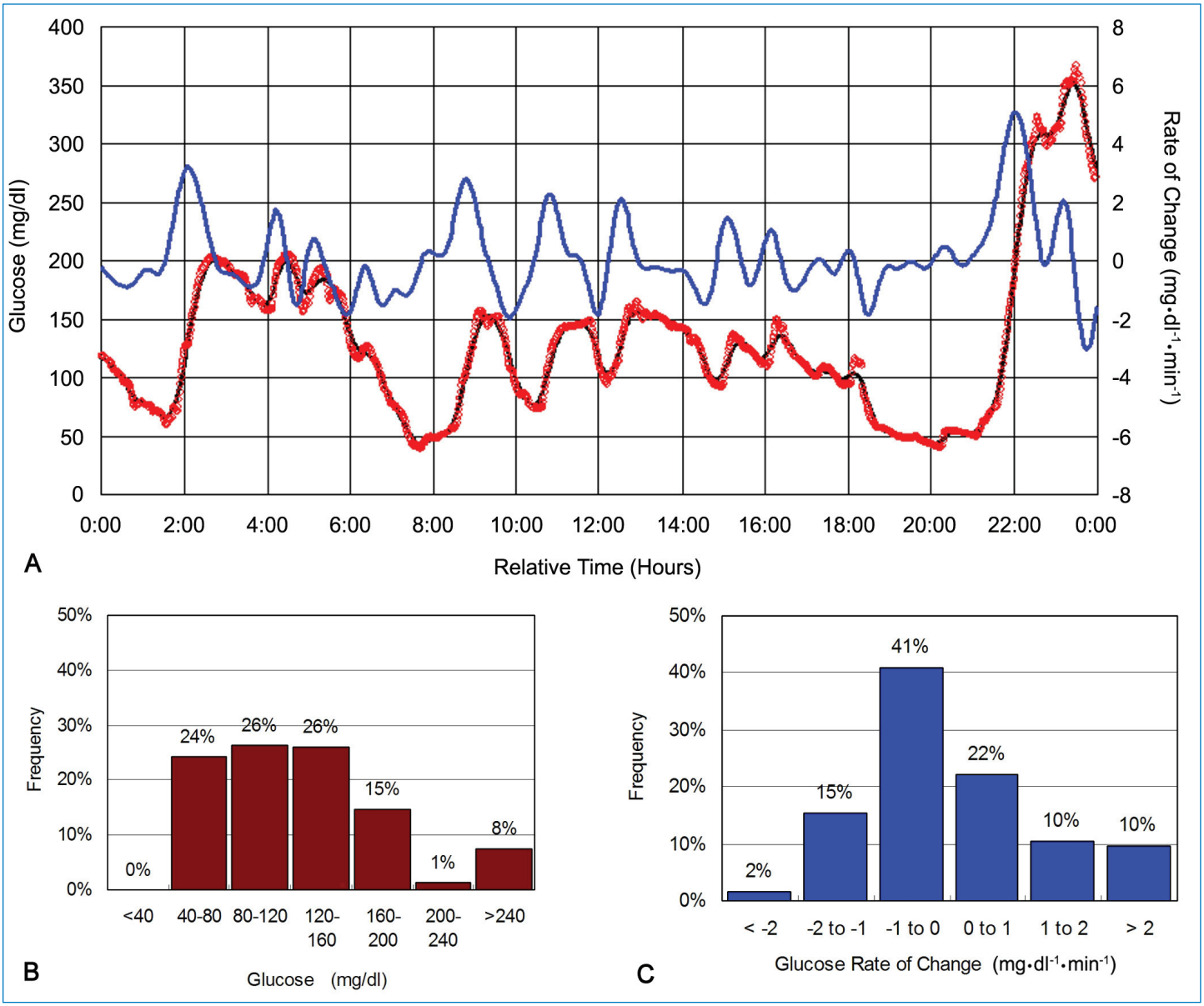

Figure 1. **(A)** The imported 1-minute FreeStyle Navigator continuous glucose profile is shown as red open circles. Filtered data, used to calculate the glucose rate of change, are shown as an underlying solid black line. The glucose rate of change is shown as a solid blue line. **(B)** The distribution of glucose values is reported in 40 mg/dl bins. **(C)** The distribution of glucose rates of change is reported in 1 mg•dl^{-1}•min^{-1} bins from -2 to 2 mg•dl^{-1}•min^{-1}.

demonstrate that the glucose rate-of-change distribution of a data set significantly affects the measured accuracy of a continuous glucose sensor.

This concept is further demonstrated in the following example. Analysis of a glucose data set with modest rates of change (trace C from **Figure 3**, with 88% of all glucose rate-of-change values between -1 and 1 mg•dl^{-1}•min^{-1}) reveals that a *perfect* sensor with a 12-minute temporal offset would result in 96% of all paired glucose values falling in the Clarke A zone. However, a glucose data set with high rates of change (trace E from **Figure 3**, with only 12% of all glucose rate-of-change values between -1 and 1 mg•dl^{-1}•min^{-1}) reveals that the identical *perfect* sensor with a 12-minute temporal offset would result in only 58% of all paired glucose values falling in the Clarke A zone.

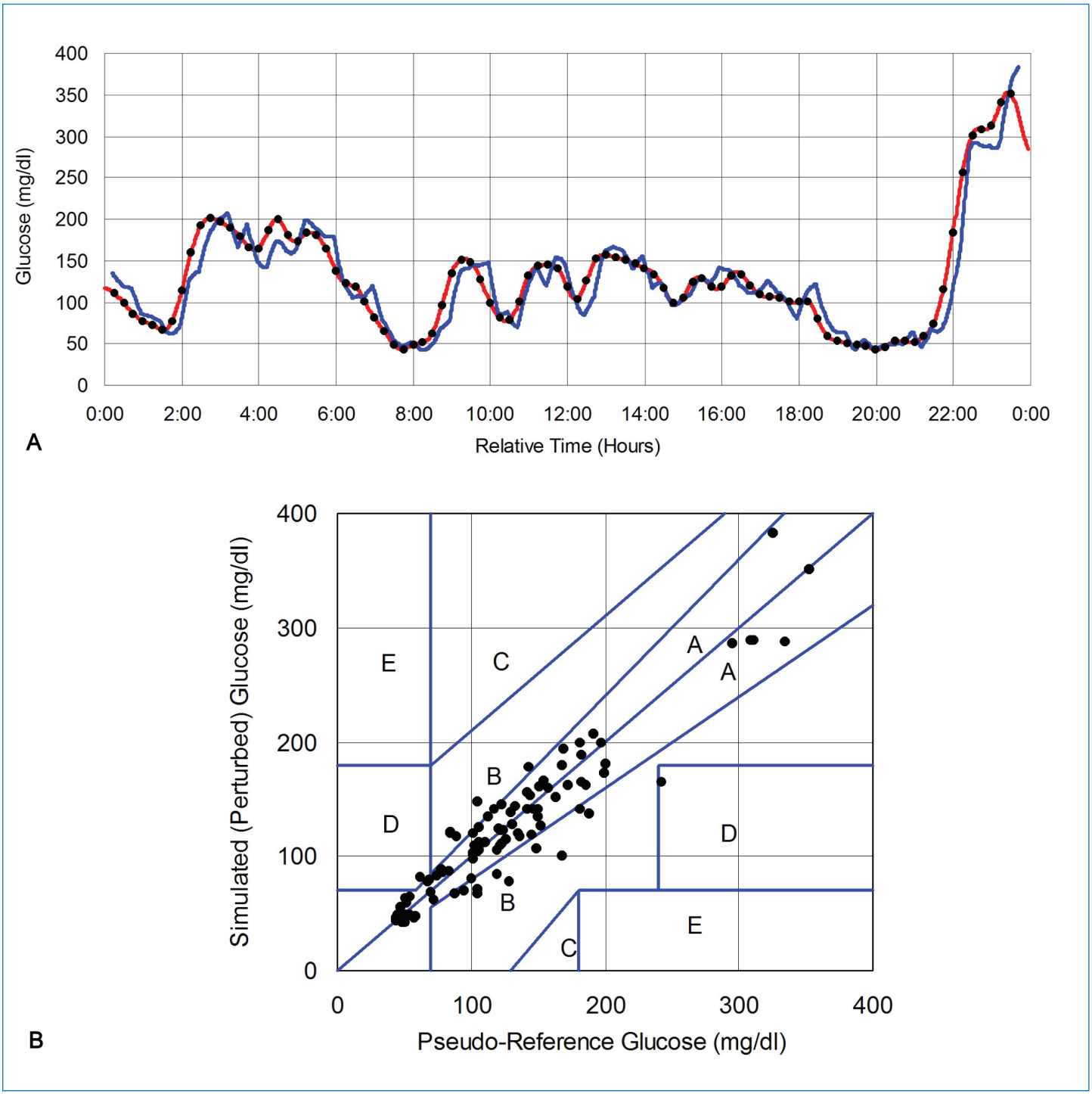

Figure 2. **(A)** The imported data set is shown in red with pseudo-reference data points indicated by black circles. The perturbed data set (20% random noise and 12-minute temporal offset) is shown in blue. Typical results are shown. **(B)** The Clarke error grid analysis of glucose data from A is presented. The displayed error grid is representative of typical results obtained from the ensemble analysis performed.

These results become even more interesting when we include the effects of 20% random noise on system performance. When 20% random noise is added to the 12-minute temporal offset, the simulated accuracy of the low rate of change glucose data set (trace C from **Figure 3**) decreases from 96 to 86%, as measured by the percentage of paired glucose values falling in the Clarke A zone. Here we see that sensor noise dominates lag at low rates of glucose change, with noise accounting for 58.1% of the sensor deviation from ideality.

However, when we look at a glucose data set with a high rate of change (trace E from **Figure 3**), the addition of 20% random noise to the 12-minute temporal offset lowers the simulated accuracy of the continuous sensor readings from 58 to 46%, as measured by the percentage of paired glucose values falling in the Clarke A zone. For these high rates of glucose change, sensor lag dominates noise, with noise accounting for 16.2% of the sensor deviation from ideality. These results are detailed in **Table 2**.

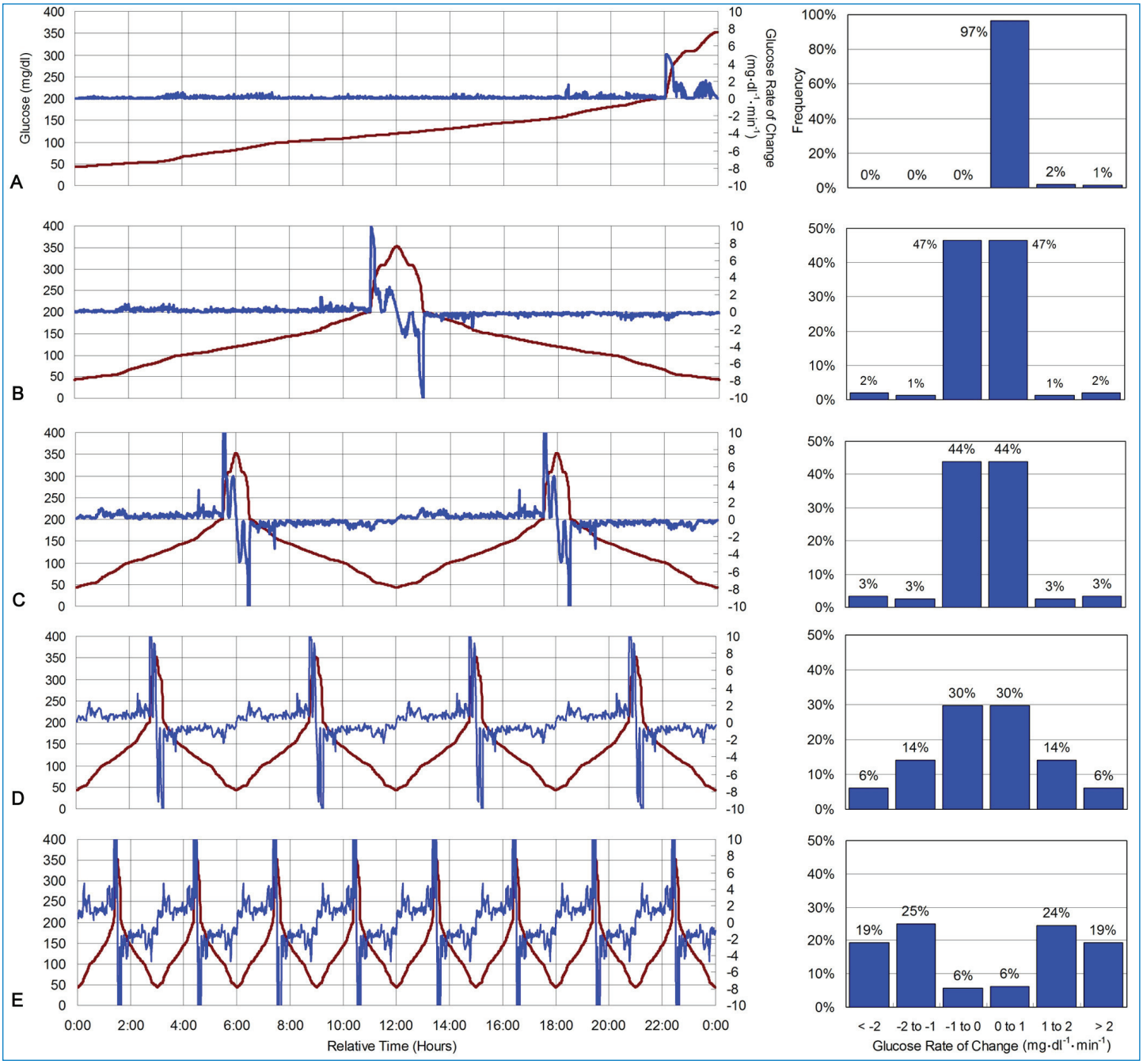

Figure 3. The glucose trace from Figure 1 has been conditioned to achieve varying glucose rate-of-change distributions. Examples are shown from top to bottom with increasing rates of change. Glucose traces are shown in red, and the glucose rate of change and rate-of-change distributions are shown in blue. All traces consist of the identical distribution of glucose values.

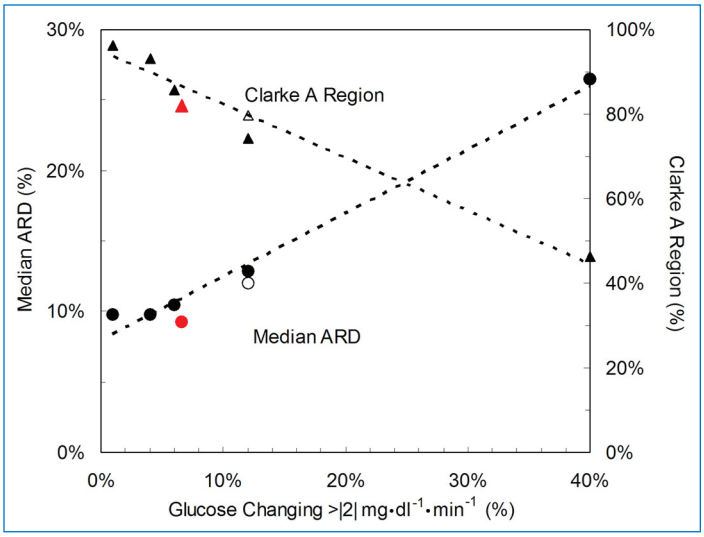

Figure 4. Median ARD (circles) and percentage of paired points falling in the Clarke A zone (triangles) are plotted versus the percentage of high rate-of-change glucose values. Black open shapes are from analysis of the imported data set with intact temporal integrity, and black closed shapes are from preconditioned data sets. All data sets have been perturbed with 20% random noise and a temporal offset of 12 minutes. Red shapes indicate the rate of change and statistical measures of accuracy observed in the 5-day in-patient study.[12]

This type of analysis can also be extended to explore the theoretical limits of accuracy of continuous glucose monitoring. Even a perfect sensor that measures glucose in the ISF will require calibration to capillary blood glucose in order to account for any concentration gradient between those two physiological compartments. Calibration itself will impart error into the system. Highly accurate home blood glucose meters have a CV of approximately 5%,[22,23] which will be reflected as approximately 10% random noise in the sensor. The lag between blood glucose and ISF glucose must also be considered.

In the previous examples offered, the applied 12-minute temporal offset accounted for both physiological and intrinsic sensor lags. *In vitro* laboratory experiments measuring the sensor response to a step change in glucose have shown that the FreeStyle Navigator sensor response time is on the order of 2 minutes. Therefore, even with an ideal sensor, imparting no intrinsic sensor lag, it is reasonable to expect that a physiological lag of approximately 10 minutes will be present.

Typical distributions of glucose rates of change for people with type 1 or type 2 diabetes requiring insulin (e.g., 75–85% of all points < ± 1 mg•dl^{-1}•min^{-1})[13,14] were modeled (using the glucose trace shown in part C of **Figure 3**). When this glucose trace is analyzed with 10% random noise and a 10-minute temporal offset, the median ARD is found to be 5.5%, with 97% of all paired points falling in the Clarke A zone.

For comparison, the FreeStyle Navigator Continuous Glucose Monitoring System was found to have a median ARD of 9.3%, with 81.7% of all paired points falling in the Clarke A zone when calibrated with capillary blood glucose using the integrated FreeStyle meter for a similar distribution of glucose rates of change.[12] This median ARD is only 3.8% higher than a simulated perfect sensor with a 10-minute physiological lag calibrated with a state-of-the-art blood glucose meter.

While the numerical simulations discussed earlier were compared to clinical data obtained using the FreeStyle Navigator sensor, this approach is not limited to any particular sensor or sensor device and was intended to minimize the sensor-specific nature of the analysis.

Table 2.
CGMetric Simulation Results (Using Data from Traces C and E from Figure 3) Are Shown Detailing Relative Contributions of Lag and Noise on Apparent Sensor Accuracy for Two Different Glucose Rate-of-Change Distributions

Applied signal perturbation	Low rate-of-change trace (88% of values between -1 and 1 mg•dl^{-1}•min^{-1})			High rate-of-change trace (12% of values between -1 and 1 mg•dl^{-1}•min^{-1})		
	Clarke A zone	Median ARD	Error contribution because of noise	Clarke A zone	Median ARD	Error contribution because of noise
12-minute temporal offset	96%	4.4%	0%	58%	22.2%	0%
12-minute temporal offset and 20% random noise	86%	10.5%	58.1%	46%	26.5%	16.2%

Conclusion

The analysis presented provides insight into the relationship between glucose rates of change and the measured accuracy of continuous glucose sensors. These numerical simulations show that the decrease in accuracy measured at high rates of change may be attributable to the effects of physiological lag rather than to any decrease in fundamental sensor performance. That is, the actual accuracy of the sensor may remain unchanged, while the measured error relative to reference blood glucose values increases because of the effect of lag associated with mass transfer between the two physiological compartments. This is consistent with expectations for a system involving time-dependent mass transfer where the intrinsic sensor lag is small compared to the relevant physiological lag between two compartments. It is important to note that that the effects of physiological lag on measured sensor accuracy may be minimized through the use of deconvolution techniques that involve reconstructing modeled plasma glucose levels from ISF glucose measurements.[24]

These results have a number of profound implications for the assessment of new continuous glucose monitoring technologies and for the design of clinical studies and regulatory reviews of those technologies.

1. When reporting accuracy measures from clinical studies, the distributions of glucose values and glucose rates of change must be detailed and direct comparisons of accuracy between studies should be limited to those with largely equivalent distributions.
2. Study designs must include physiologically relevant glucose distributions and relevant rate-of-change distributions and may include appropriate insulin and glucose challenges to achieve those distributions.
3. The measured accuracy of continuous glucose monitors may be different in certain populations characterized by greater or lesser glucose variability.
   a. Studies of continuous glucose monitoring systems in subjects with type 2 diabetes may have less glucose variability and report higher measures of accuracy than those in patients with type 1 diabetes.
   b. Studies in special populations such as children and adolescents with greater glucose variability may have lower reported measures of accuracy as a consequence of the rate of change effects described earlier.

In addition, as performance standards for continuous glucose monitoring technologies are further developed,[25] those standards should include performance goals that include references to the range of physiologically relevant distributions of glucose values and glucose rates of change. Comparisons of different continuous glucose monitoring systems should also include assessments of the glucose range and variability present in the studies.

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