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ORIGINAL ARTICLE

Characterizing Blood Glucose Variability Using New Metrics with Continuous Glucose Monitoring Data

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Abstract

Objective:

Glycemic variability contributes to oxidative stress, which has been linked to the pathogenesis of the long-term complications of diabetes. Currently, the best metric for assessing glycemic variability is mean amplitude of glycemic excursion (MAGE); however, MAGE is not in routine clinical use. A glycemic variability metric in routine clinical use could potentially be an important measure of overall glucose control and a predictor of diabetes complication risk not detected by glycosylated hemoglobin (A1C) levels. This study aimed to develop and evaluate new automated metrics of glycemic variability that could be routinely applied to continuous glucose monitoring (CGM) data to assess and enhance glucose control.

Method:

Individual 24 h CGM tracings from our clinical diabetes research database were scored for MAGE and two additional metrics designed to compensate for aspects of variability not captured by MAGE: (1) number of daily glucose fluctuations >75 mg/dl that leave the normal range (70–175 mg/dl), or excursion frequency, and (2) total daily fluctuation, or distance traveled. These scores were used to train machine learning algorithms to recognize excessive variability based on physician ratings of daily CGM charts, producing a third metric of glycemic variability: perceived variability. Finger stick A1C (average) and serum 1,5-anhydroglucitol (postprandial) levels were used as clinical markers of overall glucose control for comparison.

Results:

Mean amplitude of glycemic excursion, excursion frequency, and distance traveled did not adequately quantify the glycemic variability visualized by physicians who evaluated the daily CGM plots. A naive Bayes classifier was developed that characterizes CGM tracings based on physician interpretations of tracings. Preliminary results suggest that the number of excessively variable days, as determined by this naive Bayes classifier, may be an effective way to automatically assess glycemic variability of CGM data. This metric more closely reflects 90-day changes in serum 1,5-anhydroglucitol levels than does MAGE.

continued →

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Abbreviations: (A1C) glycosylated hemoglobin, (AUC) area under the curve, (CGM) continuous glucose monitoring, (MAGE) mean amplitude of glycemic excursion, (PGF2) urinary 8-iso-prostaglandin F2 alpha excretion; (PV) perceived variability

Keywords: blood glucose measurement, continuous glucose monitoring, glycemic control, glycemic variability, machine learning, naive Bayes classifiers

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Abstract cont.

Conclusion:

We have developed a new automated metric to assess overall glycemic variability in people with diabetes using CGM, which could easily be incorporated into commercially available CGM software. Additional work to validate and refine this metric is underway. Future studies are planned to correlate the metric with both urinary 8-iso-prostaglandin F2 alpha excretion and serum 1,5-anhydroglucitol levels to see how well it identifies patients with high glycemic variability and increased markers of oxidative stress to assess risk for long-term complications of diabetes.

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Introduction

Poorly controlled diabetes mellitus is associated with multiple long-term complications that contribute to increased morbidity and mortality. The pathogenesis of these complications is complex and involves multiple mechanisms, with chronic hyperglycemia being the principal contributor.[1,2] The role of glycemic variability and the induction of oxidative stress in the pathogenesis of complications is currently the subject of significant interest.[3–8] In investigating this role, one challenge is in definitively measuring glycemic variability. A standard means of quantifying glycemic variability, integrated with continuous glucose monitoring (CGM) systems, would further this investigation as well as facilitate clinical diabetes management.

Measuring glycemic variability is not a new concept. First proposed in 1970 by Service and colleagues,[9] the mean amplitude of glycemic excursion (MAGE) attempted to quantify glucose variability. There have since been several proposed measures, including standard deviation, mean of daily differences, continuous overlapping net glycemic action over an *n*-hour period, and average daily risk range, just to name a few.[10–13] However, none has clearly emerged as the best overall indicator of glycemic variability.[13] While definitively measuring glycemic variability has proven to be difficult, diabetes specialists clearly recognize excessive variability when they see it in CGM charts. Therefore, a novel approach was adopted in this work to incorporate physician perception into an automated metric using machine learning algorithms. The resulting metric, once refined and validated, could be incorporated into existing CGM system software to supplement glycosylated hemoglobin (A1C) as a routine assessment of overall glucose control.

This work was undertaken as part of the 4 Diabetes Support System™ studies. The 4 Diabetes Support System is an experimental system prototype that automatically detects problems in blood glucose control and suggests therapeutic changes to improve control in patients with type 1 diabetes on insulin pump therapy with CGM.[14–16] While this system can accurately detect numerous glucose control problems (hyperglycemia and hypoglycemia), our initial attempts to automatically detect excessive glycemic variability were not satisfactory. In particular, when MAGE was used as the detection criterion, our physicians, Frank L. Schwartz and Jay H. Shubrook, sometimes disagreed with system designations of excessive variability and sometimes noted actual excessive variability that went undetected by the system. This led to a consideration of the quantifiable aspects of glycemic variability as they relate to physician perception of variability and to the development of the metric reported herein.

Methods

Patients and Continuous Glucose Monitoring Data

Data for this study came from 11 patients with type 1 diabetes on insulin pump therapy participating in the 4 Diabetes Support System studies.[14–16] The 9 female and 2 male patients ranged in age from 26 to 67 years, and A1C levels ranged between 7.0% and 9.5%, with some patients considered to have excellent glucose control and others not even close to target levels. All patients used Medtronic Paradigm® insulin pumps with REAL-Time continuous glucose monitors. Patients were instructed to calibrate three times a day—before breakfast, lunch, and bedtime—when glucose levels were between 60 and 240 mg/dl. The CGM data were extracted from the

Medtronic CareLink® database into our clinical diabetes research database. Each patient supplied 3 months' worth of CGM data in all. Three hundred fifty different daily CGM charts, selected to exhibit a wide range of glycemic variability, were used to develop and test the new metrics. The 24 h data included in each chart ran from midnight of one day to midnight of the next.

Serum 1,5-anhydroglucitol (GlycoMark) and A1C

Serum levels of 1,5-anhydroglucitol (GlycoMark™) and A1C scores were routinely obtained for all participating patients on the first and last days of the 3-month CGM data collection period in our studies. These were used as clinical markers of overall glucose control for comparison. Glycosylated hemoglobin is a measure of overall glucose exposure, while GlycoMark values reflect postprandial glucose excursions. There is an inverse relationship between GlycoMark levels and postprandial glucose excursions, as higher GlycoMark scores indicate lower postprandial glucose peaks.[17] These tests were performed by LabCorp™. Note that GlycoMark scores do not reflect downward excursions leading to hypoglycemia and are therefore an incomplete measure of variability. Urinary 8-iso-prostaglandin F2 alpha excretion (PGF2), a marker of oxidative stress,[18,19] would be useful for comparison; however, PGF2 was not routinely measured as part of the 4 Diabetes Support System studies.

Mean Amplitude of Glycemic Excursion, Excursion Frequency, and Distance Traveled

Mean amplitude of glycemic excursion is the original medical measurement for variability[9] and is still considered to be the best available clinical metric for assessing glycemic variability.[13] It is known to correlate with PGF2 and GlycoMark. Mean amplitude of glycemic excursion computes the average height of glucose excursions that exceed the standard deviation for a given day. It includes only peak-to-nadir or nadir-to-peak excursions in its calculation, depending on which type of excursion occurs first in the day's data. Programmed versions of MAGE vary in forms of implementation, which may be viewed as one of its drawbacks.[13] Our implementation follows the original specification.[9] **Figure 1** demonstrates how MAGE is calculated for an actual daily CGM chart.

The 75-point excursion frequency measurement was created to address two aspects of variability that MAGE does not take into account. First, MAGE does not consider the frequency of significant excursions, only the mean of the amplitudes. Second, MAGE does not consider whether or not the glycemic excursions are out of the normal range. For example, in **Figure 1**, the first excursion is entirely within the normal range, the second is entirely in the hyperglycemic range, and the third goes from hyperglycemic to normal. At this time, we do not know which aspect of the glucose excursion (amplitude, frequency, or rate of change) is responsible for inducing the most oxidative stress in persons with diabetes, but we expect fluctuation within the normal range to be less stressful than fluctuation outside it, so we developed this metric to supplement MAGE. Excursion frequency counts the number of glucose excursions that leave the normal range over the course of one day, beginning at midnight. For implementation purposes, we arbitrarily set the amplitude of excursion to 75 mg/dl and the normal range to 70–175 mg/dl. **Figure 2** shows how excursion frequency is calculated.

The distance traveled metric is the sum of the absolute difference in glucose levels for one day of consecutive

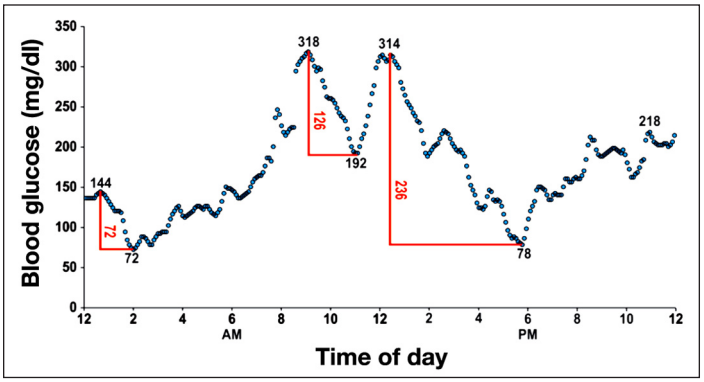

Figure 1. Example of MAGE calculation. For this 24 h CGM chart, the standard deviation is 63. The distance from the first peak (144) to the first nadir (72) is 72, which is greater than 63, so only peak-to-nadir excursions are counted. The second excursion, from 318 to 192, measures 126. The third excursion, from 314 to 78, measures 236. Mean amplitude of glycemic excursion is then (72 + 126 + 236)/3, or 145.

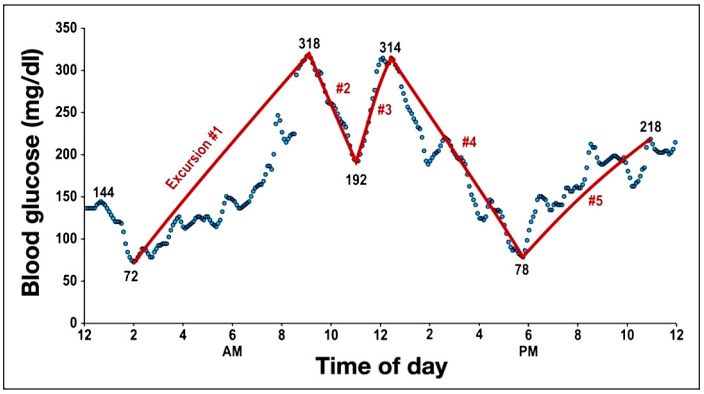

Figure 2. Example of excursion frequency calculation. The first dip, from 144 to 72, is less than 75 mg/dl, so it is not counted. Counted excursions are from 72 to 318, from 318 to 192, from 192 to 314, from 314 to 78, and from 78 to 218, yielding an excursion frequency score of 5.

CGM readings. It does not directly calculate frequency or magnitude (amplitude) of excursions; instead, it quantifies the total change in blood glucose levels throughout the day by measuring the total distance from point to point in a daily CGM plot. Thus the greater the distance traveled, the greater the variability. **Figure 3** illustrates the distance traveled calculation. The total fluctuation measured by distance traveled is another aspect of variability not directly captured by MAGE. Consider the hypothetical CGM plot shown in **Figure 4**, which was constructed by duplicating the actual blood glucose points shown in **Figures 1**, **2**, and **3**. Distance traveled goes from 1496 to 3064, reflecting the intuition that there is now twice as much variability in the chart, whereas MAGE only goes from 145 to 157. This is because the standard deviation remains the same (63), and the amplitudes of the excursions are the same, except for one larger excursion in the middle of the chart artificially introduced by appending the duplicate data.

Distance traveled is related to area under the curve (AUC) metrics in that it captures changes in the curve delimiting the area. An important distinction is that AUC, when calculated above a threshold, reflects blood glucose level as well as glycemic fluctuation. Consider again the curve of **Figure 4**. If every glucose point were elevated by 100 mg/dl, AUC would increase but distance traveled would remain the same. It should be noted that distance traveled is adversely affected by glucose sensor error. Mastrototaro and associates[20] reported that only 75.6% of readings from sensors such as those used in this study fell within an acceptable ±20% range when used in patients with type 1 diabetes. As sensor accuracy improves, we will be better able to measure variability. In the meantime, we are exploring the use of smoothing algorithms currently used for blood glucose prediction to minimize the effect of sensor noise.[21,22]

Physician Perception of Glycemic Variability and Machine Learning Algorithms

The metrics presented earlier measure different aspects of glycemic variability. However, they do not provide a distinct "cutoff" point (such as 7.0% for A1C) delimiting excessive from acceptable glycemic variability. Based on the assumption that "you know it when you see it," machine learning techniques were explored in an effort to create a new metric and automate the detection of excessive variability from CGM data. In machine learning terms, a classifier was sought that could automatically characterize any daily CGM chart as excessively variable or not. To build the classifier, physicians Jay H. Shubrook and

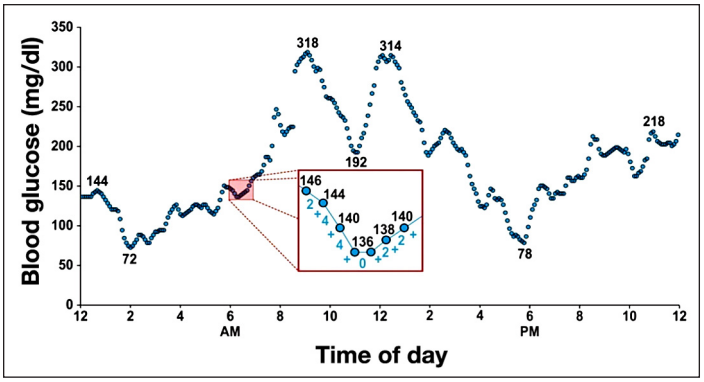

Figure 3. Example of distance traveled calculation. The CGM points are 5 min apart, so there are 287 absolute differences to sum. As a partial example, consider the CGM values between 6:00 AM and 6:30 AM, inclusive: 146, 144, 140, 136, 136, 138, 140. Then, |146–144| + |144–140| + |140–136| + |136–136| + |136–138| + |138–140| = 2 + 4 + 4 + 0 + 2 + 2 = 14. For the entire day, distance traveled = 1496.

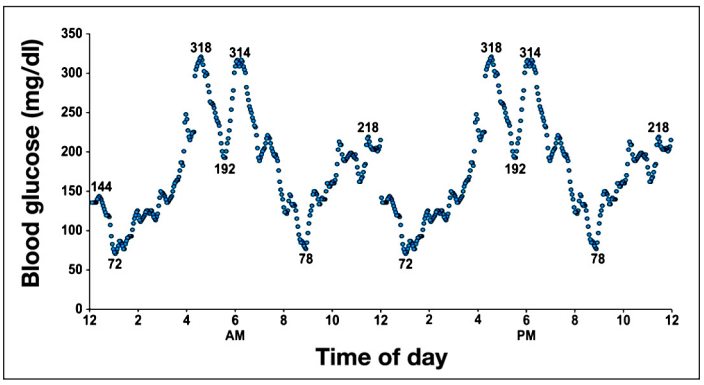

Figure 4. A hypothetical 24 h CGM chart constructed by duplicating the actual blood glucose values shown in **Figures 1, 2,** and **3**. For this chart, MAGE = 157, excursion frequency = 11, and distance traveled = 3064.

Frank L. Schwartz were asked to evaluate 250 different 24 h CGM charts from the 4 Diabetes Support System clinical research database and give their gestalt opinions as to whether each CGM chart exhibited excessive variability or not. Representative 24 h CGM charts demonstrating excessive and low glycemic variability are presented in **Figure 5**.

When both physicians agreed on whether or not a particular 24 h CGM chart exhibited excessive variability, their classification was coupled with the chart's measurements for use in training a machine learning classifier. This resulted in 218 cases of training data, which were input to Weka, a machine learning toolkit that facilitates the rapid development and evaluation of classifiers via a library of machine learning algorithms.[23] Each training example input to Weka contained MAGE, excursion frequency, and distance traveled for 24 continuous hours, from midnight to midnight, along with the physicians'

variability classification for that day. Different types of machine learning classifiers were trained and tested, using both 10-fold cross validation and a percentage-based split of 66% training, 34% testing. Ten-fold cross validation is a technique that randomly partitions the training data into 10 partitions, using nine to train the classifier and one to test. This process is repeated 10 times with a different partition used to test the classifier each time. The percentage-based split randomly partitions the data into two subsets: one contains 66% of the instances for training and the other contains the other 34% for testing.

Initially, three types of machine learning algorithms appeared to classify CGM charts most like the physicians. These were a naive Bayes classifier, a multilayer perceptron, and a logistic model tree. In brief, a naive Bayes classifier uses probabilistic reasoning, a multilayer perceptron is a type of artificial neural network, and a logistic model tree is a form of decision tree built using logistic regression. In evaluating the resultant classifiers, physicians identified their own personal classification consistency as a possible issue. While it is not hard to classify charts as distinct as those shown in **Figure 5**, charts with borderline or intermediate variability can be difficult to consistently categorize.

To select the best machine learning classifier, while accounting for consistency, a test was conducted as follows. The physicians were individually asked to classify each of 100 previously unseen daily CGM charts from the clinical diabetes research database twice, in random order. Each physician's classification was then compared to (a) his own second classification of the same chart; (b) the other physician's classification of the chart; (c) the output of the naive Bayes classifier; (d) the output of the multilayer perceptron; and (e) the output of the logistic model tree. In this test, average intraphysician consistency was 82%, with one physician consistently classifying 81 of 100 charts and the other consistently classifying 83 of 100 charts. For the 67 charts where both physicians were internally consistent, physicians agreed with each other 61 times, for an interphysician consensus of 91%.

Results

No new patient data were collected expressly for developing or evaluating the new glycemic variability metrics. This is a methods paper describing our novel approach to metric development and comparing the newly developed metrics with MAGE, which we consider to be the gold standard.

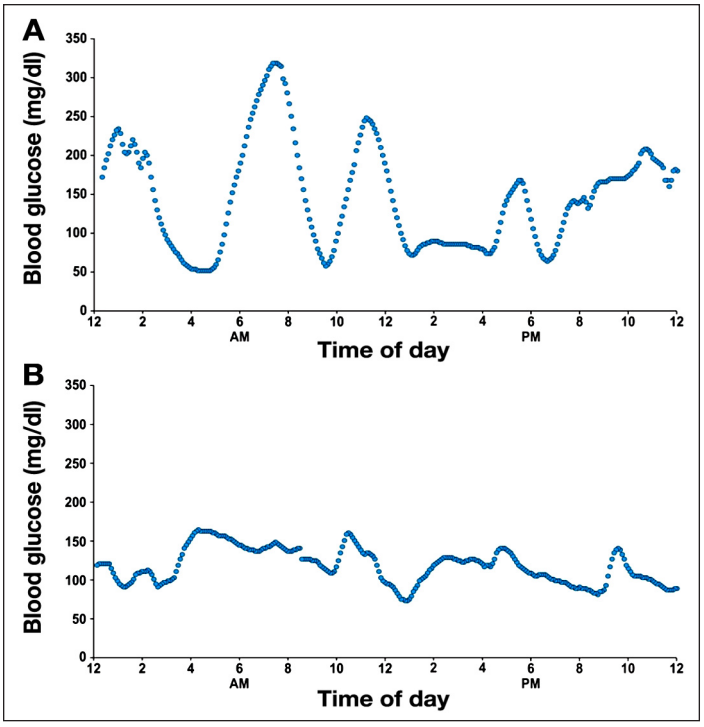

Figure 5. Representative 24 h CGM charts illustrating **(A)** excessive and **(B)** low glycemic variability. For (A), MAGE = 162, excursion frequency = 7, and distance traveled = 1730. For **(B)**, MAGE = 59, excursion frequency = 0, and distance traveled = 672.

Excursion Frequency and Distance Traveled

Initially, we designed, implemented, and evaluated two new metrics of glycemic variability—excursion frequency (**Figure 2**) and distance traveled (**Figure 3**)—and compared these with MAGE (**Figure 1**). Following initial assessment of these metrics, both Dr. Schwartz and Dr. Shubrook felt that neither they nor MAGE adequately quantified the glycemic variability that they were visualizing on the daily CGM plots. Therefore, we investigated machine learning techniques to develop additional potential metrics.

Machine Learning Classifiers

A multilayer perceptron, a logistic model tree, and a naive Bayes classifier were all tested against physician glycemic variability classifications of daily CGM charts. **Table 1** shows how the three machine learning classifiers matched the physicians' classifications for 100 daily CGM charts. The number of possible matches is the number of charts for which physicians gave consistent and/or consensus classifications. The best result is for the naive Bayes classifier, which matched the physicians' classifications 85% of the time that they were internally consistent and in agreement with each other. The number of days of CGM data classified as excessively variable for a patient by the naive Bayes classifier was selected as the perceived variability (PV) metric.

Table 1.
Comparison of Physician and Machine Learning Algorithm Classification of Excessive Variability in Daily Continuous Glucose Monitoring Charts

Comparison	Number of matches	Number of possible matches	Percentage match
Physician 1 and naive Bayes	60	83	72
Physician 1 and multilayer perceptron	52	83	63
Physician 1 and logistic model tree	52	83	63
Physician 2 and naive Bayes	68	81	84
Physician 2 and multilayer perceptron	63	81	78
Physician 2 and logistic model tree	64	81	79
Physician consensus and naive Bayes	52	61	85
Physician consensus and multilayer perceptron	47	61	77
Physician consensus and logistic model tree	46	61	75

Correlation of Perceived Variability, Mean Amplitude of Glycemic Excursion, and Glycosylated Hemoglobin with GlycoMark

Since we had A1C and GlycoMark data in the 4 Diabetes Support System clinical research database, we compared how MAGE, PV, and A1C correlated with postprandial glucose excursions (GlycoMark). **Figure 6** plots MAGE and PV against GlycoMark for the 11 patients whose data were used in this study. Values shown are from the beginning of the 3-month data collection period. There is a linear relationship between both MAGE and PV with GlycoMark scores, demonstrating that both capture post-prandial glucose excursions. Note, however, that the correlation between PV and GlycoMark is not statistically significant. Pearson correlation coefficients for MAGE, PV, and A1C with GlycoMark were -0.455 (significance, 0.034), -3.46 (significance, 0.115), and -0.598 (significance, 0.003), respectively.

Correlation of Changes in Perceived Variability, Mean Amplitude of Glycemic Excursion, and Glycosylated Hemoglobin with Changes in GlycoMark Over Time

Glycosylated hemoglobin and GlycoMark scores are also available in the 4 Diabetes Support System clinical research database for patients at the end of the 3-month data collection period. **Figure 7** plots the change in MAGE and PV from the beginning to the end of the 3-month data collection period against the change in GlycoMark scores. Over 3 months, the change in MAGE does not appear to vary with the change in GlycoMark, while the change in PV appears to reflect changes in GlycoMark. Again, for this preliminary study, the correlation between the change in PV and the change in GlycoMark is not statistically significant. Pearson correlation coefficients for change in MAGE, change in PV, and change in A1C with change in GlycoMark were -0.030 (significance, 0.931), -0.389 (significance, 0.237), and -0.756 (significance, 0.007), respectively.

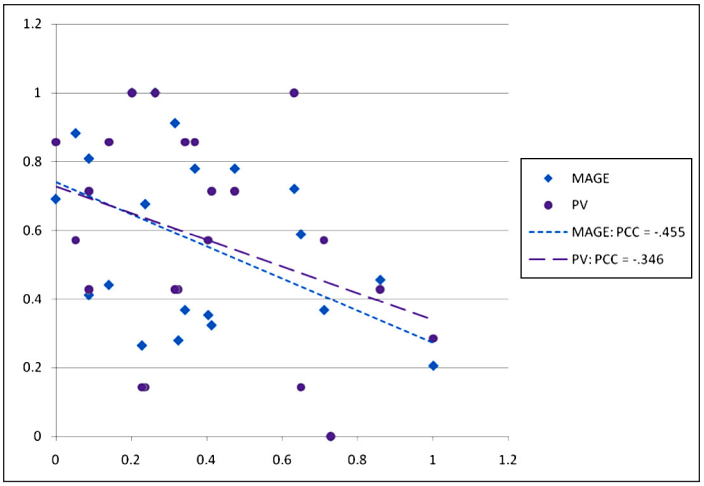

Figure 6. Mean amplitude of glycemic excursion (MAGE) and perceived variability (vertical axis) are plotted against GlycoMark (horizontal axis). Scores have been normalized to between 0 and 1 to allow for direct comparison. PCC, Pearson correlation coefficient.

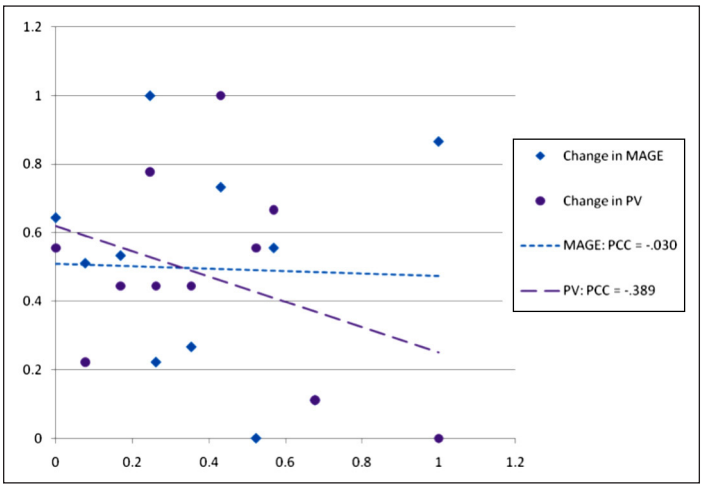

Figure 7. The change in MAGE and change in PV over a 90-day period are plotted against the change in GlycoMark. Scores have been normalized to between 0 and 1 to allow for direct comparison. PCC, Pearson correlation coefficient.

Discussion

We have developed new metrics to reflect aspects of glycemic variability that are not captured by MAGE. We describe a novel approach to incorporating physician perception of glycemic variability into an automated PV metric using machine learning algorithms. The resulting PV metric is very preliminary and based on only two physicians' perceptions of glycemic variability. However, we plan to use multiple volunteer diabetes experts to interpret 24 h CGM plots to increase the robustness of our naive Bayes classifier. Once refined and validated, this metric could be incorporated into existing CGM system software to supplement A1C as a routine assessment of overall glucose control and risk for long-term complications.

While work is ongoing to refine and evaluate the new metrics, it is clear that the naive Bayes classifier and other machine learning tools in the Weka toolkit provide a promising platform for understanding and measuring glycemic variability. To further develop the PV metric, we plan to (a) quantify additional aspects of variability, such as how rapidly blood glucose rises or falls during excursions, and correlate these measures with PGF2; (b) solicit additional diabetes experts to classify CGM plots as excessively variable or not, to acquire more training examples for machine learning algorithms; and (c) train and test additional machine learning algorithms.

Following further development, we will conduct *in silica* experiments on data from a larger patient population to determine which factors, in which combination, best agree with physician perception and best correlate with physiological markers of glycemic variability and oxidative stress, including PGF2. Results will be used to refine the new metric, which could potentially aid in identifying the role of glycemic variability in the pathogenesis of diabetes complications as well as providing a practical tool for clinical assessment.

Conclusions

New glycemic variability measurements have been developed to augment the capabilities of MAGE and to correspond to gestalt physician interpretation of daily CGM charts. Preliminary results for a novel machine learning approach to glycemic variability assessment are promising. The new PV metric could be incorporated into existing CGM software to potentially supplement A1C as a routine measure of overall glucose control. However, this work is a proof of concept, and the metric needs further refinement and evaluation before being introduced as a clinical tool. Additional work to enhance and validate the new metric is underway. Clinicians willing to participate in this research by giving their gestalt impressions of daily CGM charts, via an experimental Web site, are invited to contact Dr. Frank Schwartz (schwartf@ohio.edu) for additional information.

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Disclosure:

The software and methodology implemented in the 4 Diabetes Support System have been submitted to the U.S. patent office, application number US60/901,703, and rights are co-owned by the Ohio University Technology Transfer Office, Dr. Marling, and Dr. Schwartz.

Acknowledgments:

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