

A Consensus Perceived Glycemic Variability Metric

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Abstract

Objective:

Glycemic variability (GV) is an important component of overall glycemic control for patients with diabetes mellitus. Physicians are able to recognize excessive GV from continuous glucose monitoring (CGM) plots; however, there is currently no universally agreed upon GV metric. The objective of this study was to develop a consensus perceived glycemic variability (CPGV) metric that could be routinely applied to CGM data to assess diabetes mellitus control.

Methods:

Twelve physicians actively managing patients with type 1 diabetes mellitus rated a total of 250 24 h CGM plots as exhibiting low, borderline, high, or extremely high GV. Ratings were averaged to obtain a consensus and then input into two machine learning algorithms: multilayer perceptrons (MPs) and support vector machines for regression (SVR). *In silico* experiments were run using each algorithm with different combinations of 12 descriptive input features. Ten-fold cross validation was used to evaluate the performance of each model.

Results:

The SVR models approximated the physician consensus ratings of unseen CGM plots better than the MP models. When judged by the root mean square error, the best SVR model performed comparably to individual physicians at matching consensus ratings. When applied to 262 different CGM plots as a screen for excessive GV, this model had accuracy, sensitivity, and specificity of 90.1%, 97.0%, and 74.1%, respectively. It significantly outperformed mean amplitude of glycemic excursion, standard deviation, distance traveled, and excursion frequency.

Conclusions:

This new CPGV metric could be used as a routine measure of overall glucose control to supplement glycosylated hemoglobin in clinical practice.

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Abbreviations: (4DSS) 4 Diabetes Support System, (CGM) continuous glucose monitoring, (CPGV) consensus perceived glycemic variability, (DT) distance traveled, (EF) excursion frequency, (GV) glycemic variability, (HbA1c) glycosylated hemoglobin, (MAE) mean absolute error, (MAGE) mean amplitude of glycemic excursion, (ML) machine learning, (MP) multilayer perceptron, (RMSE) root mean square error, (SD) standard deviation, (SVR) support vector machines for regression, (T1DM) type 1 diabetes mellitus

Keywords: blood glucose measurement, continuous glucose monitoring, glycemic control, glycemic variability, machine learning, support vector regression

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Introduction

Glycemic variability (GV) is an important component of overall glycemic control in patients with diabetes mellitus. In a 2013 report, an expert panel of diabetes specialists recommended including a measure of GV on standardized glucose reports to augment the current use of glycosylated hemoglobin (HbA1c).¹ The panel's recommendations were focused on improving glycemic control in individuals with type 1 diabetes mellitus (T1DM) through better utilization of continuous glucose monitoring (CGM) data. Citing other studies,²⁻⁸ the panel argued that the most compelling reasons to identify and work to minimize GV are (a) increased GV is associated with poor glycemic control² and (b) increased GV is a strong predictor of hypoglycemia,^{3,4} which has been linked to excessive morbidity and mortality.⁵⁻⁸ While panelists agreed on the importance of GV measurement, they noted that there is no current consensus on the best GV metric to use or on the boundary that delineates acceptable from excessive GV.

Service and coauthors⁹ first proposed the mean amplitude of glycemic excursion (MAGE) as a measure of GV in 1970, and since then, a large number of additional GV metrics have been proposed without any agreed upon successor to MAGE.¹⁰ Rodbard¹¹ points out that this multiplicity of metrics makes linking GV measurement to diabetes complications a major challenge, and as a result, there have been calls for standardizing one or a few metrics.^{12,13} A standardized GV metric could facilitate investigation of the impact of GV on risk for diabetes complications, as well as aid in the clinical assessment of GV.

While formally measuring GV in the clinical setting is challenging, physicians are able to recognize excessive or acceptable GV when they see it in CGM plots. Therefore, we have adopted a different approach to GV measurement that leverages supervised machine learning (ML) algorithms to capture this gestalt physician perception. Machine learning methods are designed to take input features [e.g., MAGE and standard deviation (SD)] related to the target output (e.g., GV) and combine them into a parameterized metric that outperforms any of the individual input features at the task of characterizing the target variable. Here, we present a consensus perceived glycemic variability (CPGV) metric that could be applied to CGM data for both direct patient care and clinical research studies.

This work builds upon a foundation laid in two earlier studies in which ML models were built to match physician perception of 24 h CGM plots as exhibiting excessive or acceptable GV.^{14,15} In a preliminary study, we built a naive Bayes classifier based only on MAGE and two other features, which matched physician perception 85% of the time.¹⁴ In a second study, we smoothed CGM data to mitigate sensor inaccuracies, introduced additional features to characterize CGM plots, and experimented with additional ML algorithms.¹⁵ These enhancements resulted in a multilayer perceptron (MP) that matched physician perception 93.8% of the time. These studies provided proof of concept but were limited in that they included the perceptions of only the two physician authors (Jay H. Shubrook and Frank L. Schwartz) and used only a binary classification scheme (excessive versus acceptable GV). Now we have a consensus metric derived from the GV interpretations of 12 diabetes specialists, who rated GV on a scale of low, borderline, high, or extremely high.

Methods

Physician Participants

Physicians actively managing patients with T1DM on insulin pump therapy were recruited to help develop a new CPGV metric at the 2011 Diabetes Technology Meeting. Nine Diabetes Technology Meeting attendees plus three other qualifying physicians volunteered to rate CGM plots for this study. Participants had a range of 5 to 40 (mean 23.7) years of experience specifically managing T1DM patients and reported that they currently managed 10 to 500 (mean 169) patients.

Continuous Glucose Monitoring Plots

The CGM data was supplied by a pre-existing database built during earlier studies to develop the 4 Diabetes Support System™ (4DSS).¹⁶⁻¹⁸ The 4DSS is an experimental system prototype that automatically detects problems in blood

glucose control, identifies their probable causes, and suggests therapeutic adjustments to correct detected problems. The inability of the 4DSS to accurately detect excessive GV using existing GV metrics was the impetus for developing a new metric. The 4DSS database contains data from patients with T1DM on insulin pump therapy and CGM traces were taken from 14 female and 5 male patients, ranging in age from 17 to 71 (mean 47) years, with HbA1c between 6.7% and 11.0% (mean 8.0%). All patients used Medtronic Paradigm[®] insulin pumps with REAL-Time continuous glucose monitors and were instructed to calibrate their monitors three times a day. A total of 250 daily CGM charts, ranging from midnight of one day to midnight of the next, were selected to exhibit a wide range of GV.

Machine Learning Experiments

Twelve physicians rated 250 24 h CGM plots using a Web-based GV rating system. Each physician rated 55 or 110 plots, and each plot was rated by three or four physicians. Plots were rated as 1, low; 2, borderline; 3, high; or 4, extremely high. **Figure 1** shows sample plots that were unanimously rated by participating physicians as 1, low; 2, borderline; 3, high; and 4, extremely high. When ratings for a plot differed among physicians, they were averaged to obtain a consensus rating. Inter-rater variability was reasonably low; on average, an individual physician's rating differed from the consensus of the other raters by 0.5 on the 3-point scale of from 1 to 4.

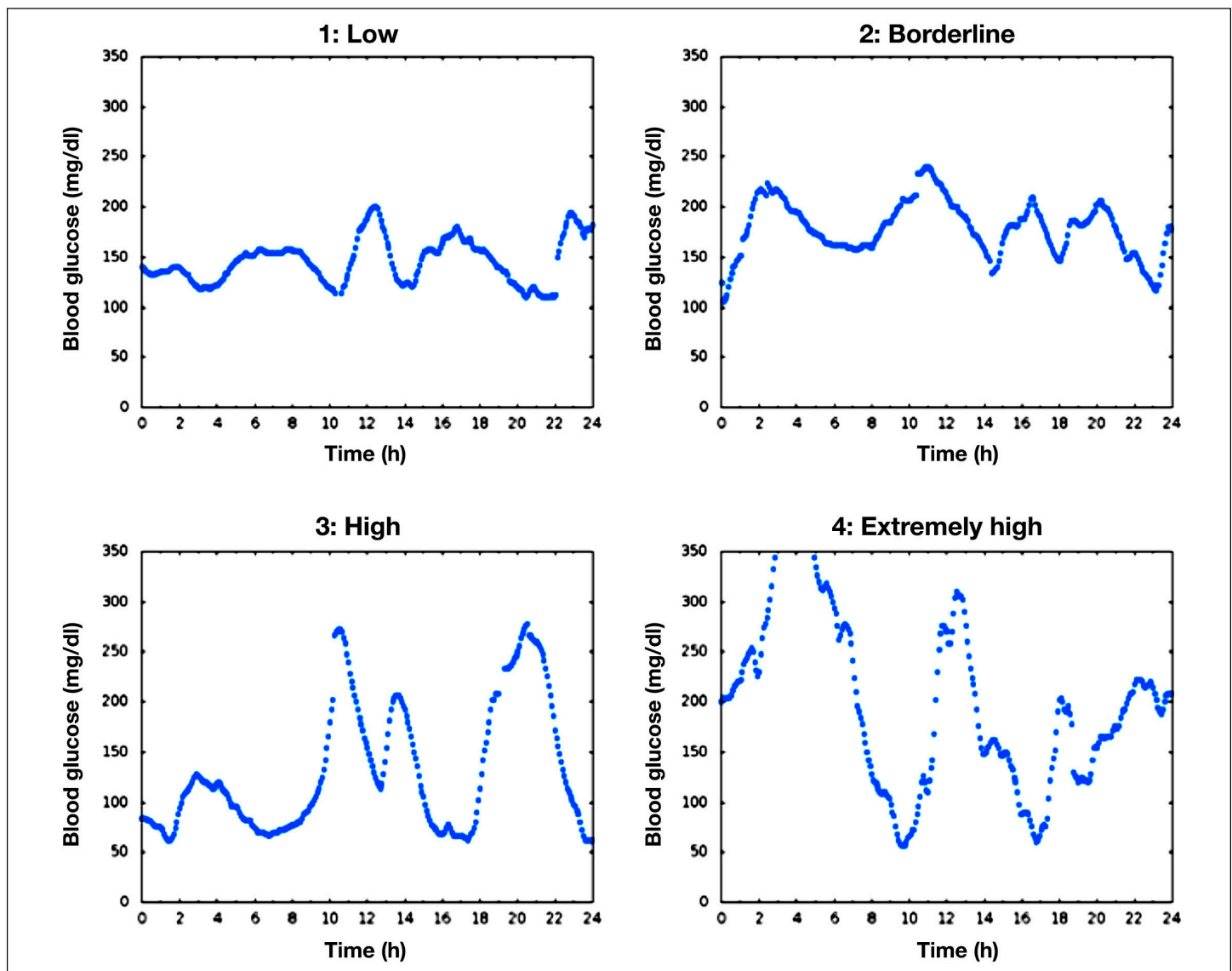


Figure 1. Sample CGM plots unanimously rated by participating physicians as 1, low; 2, borderline; 3, high; and 4, extremely high.

Machine learning models were trained to match the consensus ratings. To train an ML model, it is necessary to characterize and represent each daily CGM plot as a vector of numeric values. The consensus rating for the plot appears in the vector as the target value to be modeled. The other features in the vector are chosen to represent different aspects of the CGM plot, which, in combination, could inform the models. The following is the complete list of features used in the experiments:

1. MAGE: the mean distance between the local minima and maxima of a blood glucose plot, as originally defined by Service and coauthors.⁹ Only distances exceeding the SD of the blood glucose values are included in the aggregate.
2. Excursion Frequency (EF): the number of blood glucose excursions. Only excursions greater than 75 mg/dl with points outside the normal range are included in the count.
3. Distance Traveled (DT): the sum of the distances between each pair of consecutive CGM data points, DT captures overall fluctuation and is similar to mean absolute glucose, as described by Hermanides and coauthors.¹⁹
4. SD: the sample SD computed over the set of CGM measurements.
5. Area Under the Curve: the total area of the CGM image, defined as the region between the CGM curve and a horizontal line corresponding to the minimum blood glucose level measured for that day. With minimum blood glucose level as the baseline, area under the curve reflects fluctuation rather than glucose exposure.
6. Central Image Moments: seven central image moments of order up to 3 are computed on the CGM image. They can be used to capture useful properties of the image such as the centroid, orientation, and moment of inertia.
7. Eccentricity: the ratio between the maximum and minimum distance from the boundary of the CGM image to its centroid. Eccentricity conveys how much the shape of the image deviates from being circular, or equivalently, how elongated the image is.
8. Discrete Fourier Transform: the magnitudes of the 24 sinusoidal components with the lowest frequency from the discrete Fourier decomposition of the CGM graph.
9. Roundness Ratio: the ratio between the perimeter of the CGM image and its area.
10. Bending Energy: the average curvature of the CGM graph.
11. Direction Codes: A direction code is the absolute difference between the values of two consecutive CGM data points. These features compute the percentages of direction codes falling within specified ranges.
12. Maximum Slope: the maximum increasing slope and the maximum decreasing slope of glycemic excursions, where excursions are defined as for the EF feature.

Some of these features (e.g., MAGE and SD) are themselves measures of GV. Other features are numeric transformations more generally used in signal processing applications, regardless of the source of the signal. Since each of these general features captures only a particular aspect of the perceived GV, they are not meant to be used as standalone GV metrics. Their utility shows only in combination; hence, ML algorithms are used to develop an overall measure of GV that combines the proposed features.

The first 11 features are fully defined and motivated in our earlier papers.^{14,15} A final feature, maximum slope of glycemic excursion, was added to this study in response to clinician feedback on our prior work. The intuition behind this feature is that rapid rise or fall in blood glucose levels contributes to an overall perception of increased GV. Note that all of these features are calculated from blood glucose sensor data known to include some degree

of inaccuracy, or noise.²⁰ Smoothing algorithms, applied to the data before feature calculation, can help to mitigate the effects of this noise.²¹ All ML experiments were run on both smoothed and raw data for comparison.

The ML algorithms evaluated were MPs²² and support vector machines for regression (SVR).^{23,24} These are flexible learning models known for their abilities to accommodate multiple overlapping (collinear or otherwise interdependent) features and to approximate complex decision boundaries. We used the Weka implementation²⁵ for the MP algorithm and the Library for Support Vector Machines implementation²⁶ for the SVR.

Each model was trained and tested using 10-fold cross validation, a standard ML technique in which the data are randomly divided into 10 partitions, or folds. Nine folds are used for training, and the other is used to test; the entire process is repeated 10 times with a different fold used to test the model each time. Multiple *in silico* experiments were run to evaluate the models, using smoothed or raw CGM data, with features selected on a separate development set. Two standard ML feature selection methods were used: greedy forward selection and greedy backward elimination. Greedy forward selection begins with the single feature that provides the best accuracy and incorporates the next best features one at a time until no better accuracy can be achieved. Greedy backward elimination begins with all potential features, eliminates the feature whose exclusion best improves accuracy, and continues excluding features until no better accuracy can be obtained.

Results

Model Performance

Models were judged by their ability to output GV ratings that matched the CPGV ratings of the participating physicians. Any difference between a model's output and the CPGV rating for a CGM plot constitutes an error. Overall performance for a model is then judged by the root mean square error (RMSE) and the mean absolute error (MAE). Models were compared to each other and to the performance of individual physicians in matching the CPGV ratings.

Table 1 shows model performance. The best performance, i.e., the lowest RMSE and MAE, was for an SVR model with a Gaussian kernel using smoothed CGM data. Greedy forward selection included all of the experimental feature types, except for DT and central image moments, in this model. This model performs comparably to individual physicians at matching consensus ratings. Note that the comparison of models to physicians is necessarily less precise than the comparison of models to other models. This is, in part, because models produce floating point output while physician ratings are integers from 1 to 4. Model outputs were rounded to the nearest integer for comparison to physician ratings, as shown in **Table 1**. Additionally, an individual physician's rating may be included in the calculation of the consensus rating to be matched, boosting physician performance. Performance was calculated both with individual physician ratings included and excluded from the consensus, as shown in **Table 1**.

Table 1. Model Performance ^a				
	RMSE (floating point)	MAE (floating point)	RMSE (integer)	MAE (integer)
Best SVR model	0.417	0.316	0.511	0.376
Best MP model	0.496	0.392	0.575	0.445
Physicians (inclusive)	-----	-----	0.489	0.355
Physicians (exclusive)	-----	-----	0.699	0.509

^a Inclusive/exclusive indicates whether or not the physician's own rating was included in the consensus being matched. Models produce floating point output while physician ratings are integers from 1 to 4. Model outputs were rounded to integers for comparison.

A Screen for Excessive Glycemic Variability

The best SVR model, as the new CPGV metric, could be used as a screen for excessive GV by choosing an appropriate threshold value. Its performance as a screen was compared to that of MAGE, SD, DT, and EF. The CPGV metric

was tested against these other GV metrics by measuring accuracy, sensitivity, and specificity at classifying a separate set of 262 24 h CGM plots from the 4DSS database. The threshold used for each metric was the value that gave the best overall accuracy in distinguishing excessive from acceptable GV, computed on a separate development data set. The test plots had been rated as excessively variable or not by two physicians (Jay H. Shubrook and Frank L. Schwartz) in an earlier study.^{14,15} Results are shown in **Table 2** and **Figure 2**. The tabular data and the receiver operating characteristic curve plotted in **Figure 2** show that the new CPGV metric outperforms MAGE, SD, DT, and EF as a screen for excessive GV. As shown in **Table 2**, the improvements in accuracy and sensitivity of CPGV over the other four metrics are all statistically significant, as determined by one-tailed, paired-sample *t*-tests. The improvements in specificity are statistically significant only for SD and MAGE.

Discussion

The new CPGV metric can now automatically rate previously unseen daily CGM plots, producing ratings comparable to those of physicians, as illustrated by **Figure 3**.

The new CPGV metric is intended to augment the use of HbA1c to assess overall glucose control. **Figure 4** illustrates how CPGV ratings could be integrated with existing commercial CGM software reports or with the proposed ambulatory glucose profile recommended by Bergenstal and coauthors.¹ It also shows how CPGV ratings can be aggregated for as many days of CGM data as are available to aid in the review and visualization of GV trends. Note that data sufficiency from CGM devices is a prerequisite for use of the CPGV. In **Figure 4**, no CPGV is calculated for the first Wednesday of the example, due to an insufficient number of CGM data points for that day.

The illustrative GV overview shown in **Figure 4** suggests only the type of trends analysis that is currently available for glucose exposure and proposed for GV. Should advanced decision support systems, such as the 4DSS,^{16–18} become more commonly used in practice, then other GV trends, tied to life events, might also be highlighted by such an overview. For example, patients may experience changes in GV patterns during menstrual cycles, sports seasons, final exam periods, holidays, and so on.

As previously noted, the CPGV metric is only applicable when sufficient CGM data are available. While multiple days of CPGV ratings may be aggregated, the metric is limited in that it is not defined over partial days of CGM data or for self-monitoring of blood glucose (finger stick) data. A further limitation is that the metric was designed for patients with T1DM. For use with type 2 diabetes mellitus, another ML study could be conducted in which CGM plots from patients with type 2 diabetes mellitus are rated by expert clinicians specializing in their care. Additionally, as is

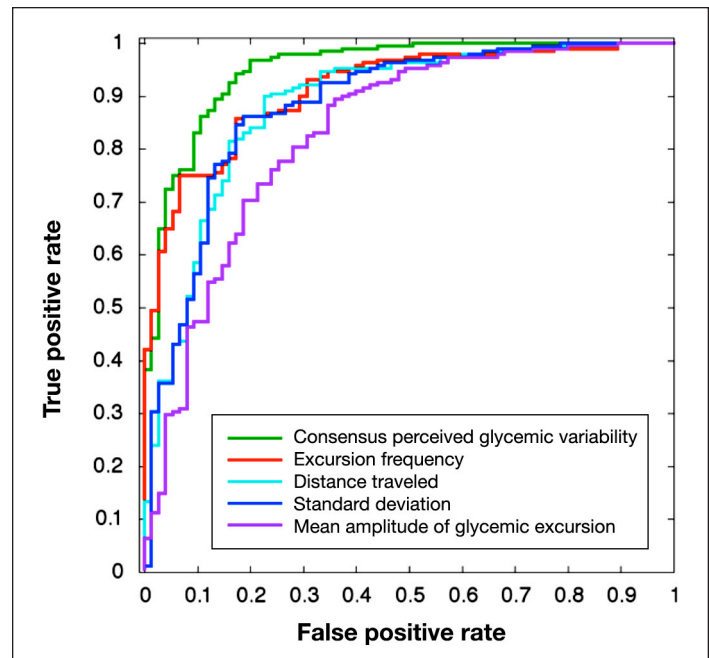


Figure 2. The receiver operating characteristic curve shows that the new CPGV metric provides a better screen for excessive GV than EF, DT, SD, or MAGE.

Table 2.
Results of the Consensus Perceived Glycemic Variability Metric Compared with Other Metrics^a

	Accuracy	Sensitivity	Specificity
CPGV	90.1%	97.0%	74.1%
EF	84.3% <i>p</i> < .005	92.0% <i>p</i> < .05	66.1% ns
DT	83.9% <i>p</i> < .005	89.1% <i>p</i> < .005	72.3% ns
SD	83.6% <i>p</i> < .001	91.6% <i>p</i> < .005	64.8% <i>p</i> < .05
MAGE	80.8% <i>p</i> < .001	90.9% <i>p</i> < .05	56.7% <i>p</i> < .005

^a The new CPGV metric provides a more accurate, sensitive, and specific screen for excessive GV than EF, DT, SD, or MAGE. The statistical significance of the improvement of CPGV over the other metrics, as determined by one-tailed, paired-sample *t*-tests, is shown, where ns indicates no statistical significance.

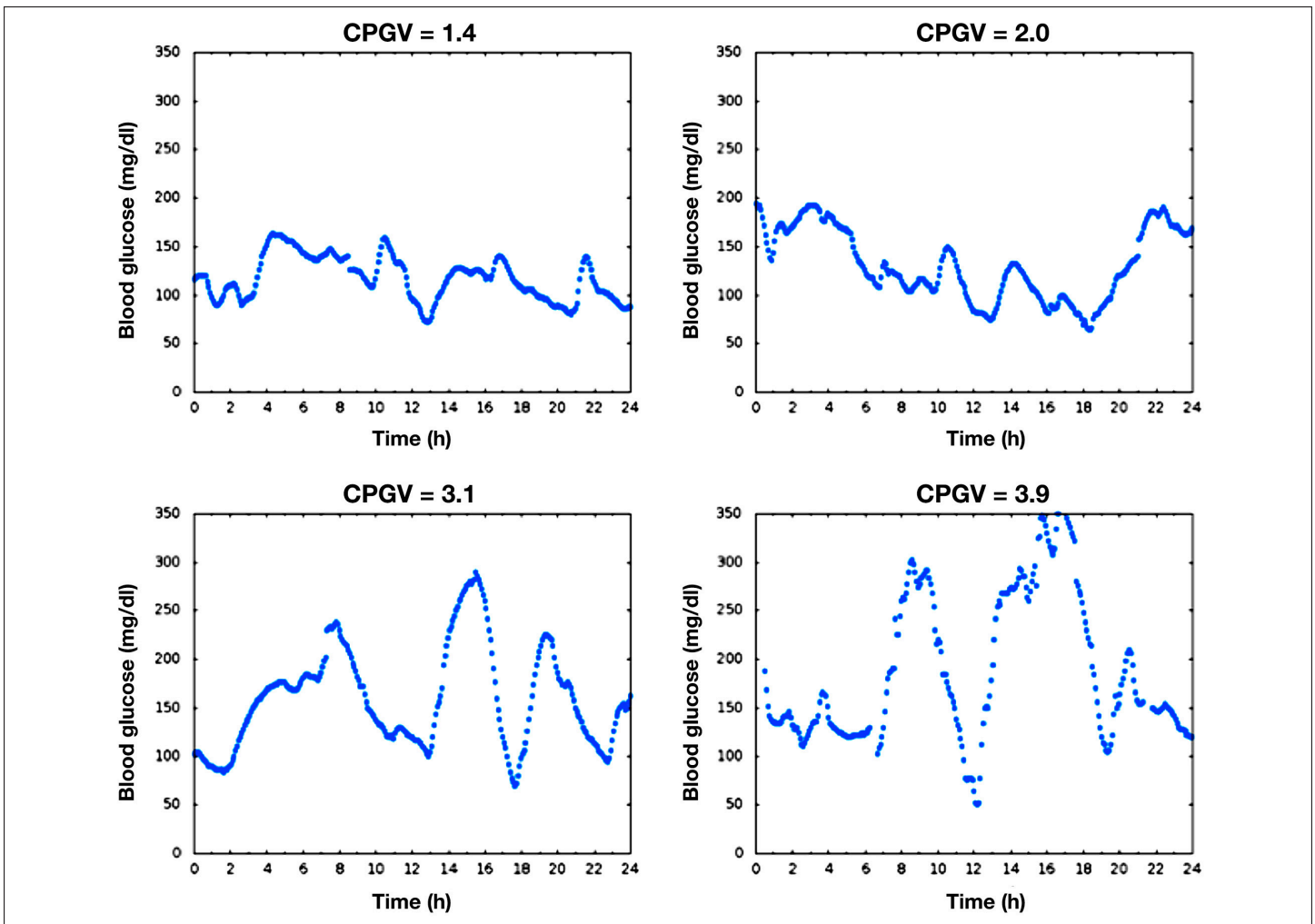


Figure 3. Automatically computed CPGV ratings for sample CGM plots that were not used in training the model.

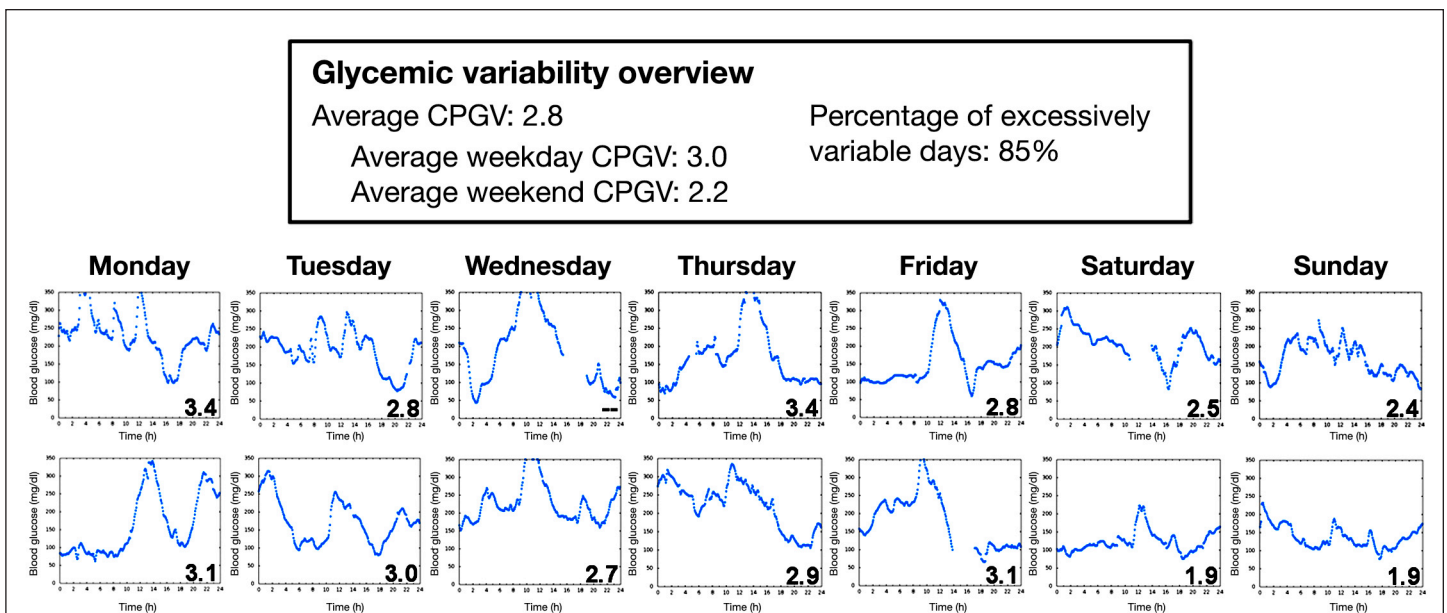


Figure 4. A GV overview, which could be incorporated in existing commercial CGM software reports or the proposed ambulatory glucose profile. Here, 14 days of data are shown as an example; daily CPGV values can be aggregated for as many days of CGM data as are available.

true for all GV metrics, a link between high CPGV ratings and diabetic complications has not yet been established. No patient outcomes data were considered as part of this study.

We hope that the new metric will aid in the ongoing investigation of the linkage between GV and complications in patients with T1DM. We are currently performing a small clinical study of patients (adults and adolescents) with T1DM and measuring serum markers of oxidative stress, including urinary 8-iso-PGF2 alpha, to compare with CPGV and other GV metrics, seeking correlation. We would gladly run our new metric on any clinical CGM databases containing clinical markers of oxidative stress and/or complication outcomes for retrospective study.

Conclusions

There is a clinical need to be able to identify patients with excessive GV, and yet there is no automated screen in routine clinical use. We have developed a CPGV metric that captures the gestalt perceptions of 12 experienced physicians actively managing patients with T1DM. This metric distinguishes excessive from acceptable GV significantly better than MAGE, SD, DT, or EF. The new CPGV metric could be incorporated into existing CGM software or proposed standardized glucose reports and used as a routine measure of overall glucose control to supplement HbA1c in clinical practice.

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