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Calculating the Mean Amplitude of Glycemic Excursion from Continuous Glucose Monitoring Data: An Automated Algorithm

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Abstract

Background: Glycemic variability is currently under scrutiny as a possible predictor of the complications of diabetes. The manual process for estimating a now classical measure of glycemic variability, the mean amplitude of glycemic excursion (MAGE), is both tedious and prone to error, and there is a special need for an automated method to calculate the MAGE from continuous glucose monitoring (CGM) data.

Methods: An automated algorithm for identifying the peaks and nadirs corresponding to the glycemic excursions required for the MAGE calculation has been developed. The algorithm takes a column of timed glucose measurements and generates a plot joining the peaks and nadirs required for estimating the MAGE. It returns estimates of the MAGE for both upward and downward excursions, together with several other indices of glycemic variability.

Results: Details of the application of the algorithm to CGM data collected over a 48-h period are provided, together with graphical illustrations of the intermediate stages in identifying the peaks and nadirs required for the MAGE. Application of the algorithm to 104 CGM datasets (92 from children with diabetes and 12 from controls) generated plots that, on visual inspection, were all found to have identified the peaks, nadirs, and excursions correctly.

Conclusions: The proposed algorithm eliminates the tedium and/or errors of manually identifying and measuring countable excursions in CGM data in order to estimate the MAGE. It can also be used to calculate the MAGE from "sparse" blood glucose measurements, such as those collected in home blood glucose monitoring.

Introduction

Quantifying the short-term variability of blood glucose concentration or interstitial fluid glucose is an important requirement for research studies examining the relationship of glycemic variability to diabetes complications such as oxidative stress[1] and macro- and microvascular pathology.[2,3]

Several measures of glycemic variability have been proposed, and their relative merits have been the subject of recent reviews.[4–7] The computation of most of these measures is straightforward, but the mean amplitude of glycemic excursion (MAGE)[8–10] requires manual computation, which is both tedious and prone to operator error.

The MAGE is a simple arithmetic average of the "amplitudes" of all glycemic excursions greater than a prespecified threshold size (typically 1 SD, although other thresholds could, and probably should, be tested). Because glycemic excursions are rarely symmetrical, Service and co-workers[8–10] suggested their amplitudes be estimated by the magnitude of either the upward shift or the downward shift of each excursion—with the direction of the first countable excursion determining the "rule" for the remainder of that subject's data.

Although several difficulties and potential shortcomings of the MAGE have been discussed recently,[4–7] and while there are still unresolved questions as to its ability to predict the adverse consequences of high glycemic variability, the MAGE has enjoyed the status of being almost a "gold standard" among some clinicians and researchers. With the increasing availability of continuous glucose monitoring (CGM) data and a growing need to improve our understanding of the properties of the MAGE, an automated algorithm for calculating this index would appear to be highly desirable.

An algorithm for calculating the MAGE by hand is described in the original articles by Service and colleagues.[8–10] This work predated CGM, and the original instructions were

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intended to be applied to a relatively small and manageable number of blood glucose measurements. With CGM, however, surveillance at 5-min intervals generates 577 observations over a 48-h period—and the task of calculating a MAGE becomes somewhat tedious. Peaks and nadirs in the glucose profile must be identified, and the change in glucose concentration across each adjacent peak–nadir pair must be calculated and compared against a prespecified criterion (usually the SD for each day of measurement, or for the whole profile) in order to determine whether the excursion is eligible for inclusion in the average. Excursions that do not qualify as "countable" are subsumed in larger excursions. In order to complete this process accurately, a graphical representation of the data is essential—and while application of the rules for calculating the MAGE should result in a unique value for any given CGM profile, inexperienced observers can easily make mistakes that lead to incorrect estimates.

This communication describes an algorithm that has been developed and tested using CGM data collected from children both with and without diabetes.

The Algorithm

A MAGE algorithm may be thought of as a process that joins selected turning points from a time-ordered set of glucose concentrations with a set of straight lines whose vertical displacements are all greater than a prespecified minimum. This requires the identification of all the turning points in a subject's CGM profile and a determination of which turning points must be retained as the start or end point of a "countable" excursion—and which turning points can be discarded as uninteresting "noise" within a larger excursion. Once all the countable excursions have been identified, the MAGE is determined by the arithmetic average of the vertical displacements of all the upward excursions (MAGE+) or all the downward excursions (MAGE−). In addition, an average of all excursions, both upward and downward, designated MAGE.avge, is also calculated. A simple flowchart outlining the steps in such an algorithm is provided in Figure 1.

Small random fluctuations in CGM data can generate a large number of local maxima and minima that are of no interest. To facilitate identification of the relevant turning points, two approaches were implemented.

Approach 1: Identification of turning points using smoothing

A smoothed profile, as detailed below, can be used to define a sequence of contiguous time domains within which a search of the original *unsmoothed* data can then be performed in order to identify a sequence of alternating maximum or minimum turning points. Smoothing requires the application of some kind of "filter" to the raw data. Many filters can be used for this purpose, with the main consideration being to choose one that filters out only the local ("high frequency") fluctuations. A simple filter that has proved adequate in all CGM datasets analyzed to date is a symmetric nine-point moving average with exponentially decreasing weights (common factor, $\rho = 0.5$) on either side of the center, i.e., {(1,2,4,8,16,8,4,2,1)/46}, with the divisor of 46 being necessary to ensure the weights add to 1. Four points at either end of the CGM data cannot be filtered in this manner (unless the data are treated circularly)—but substituting a smoothed value

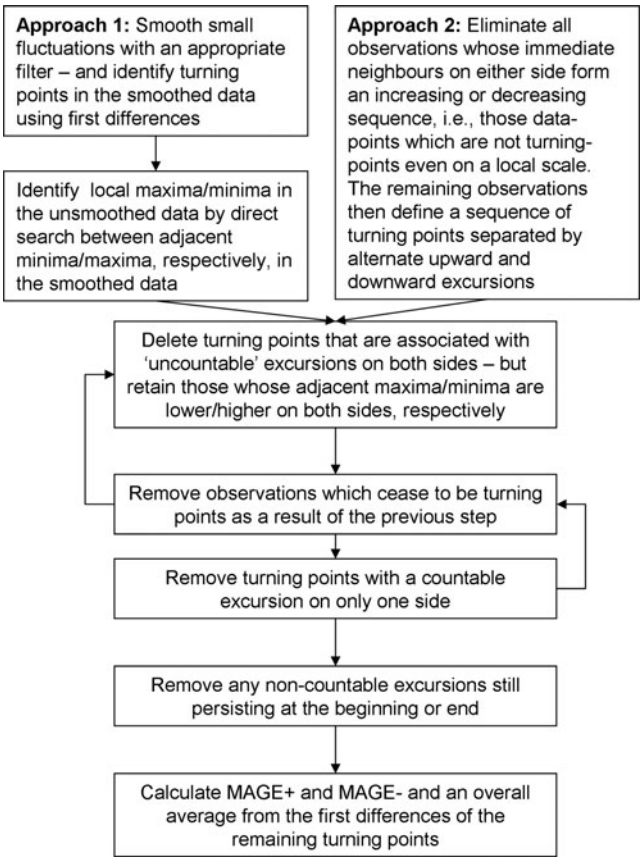

FIG. 1. Flowchart of an algorithm for calculating the mean amplitude of glycemic excursion (MAGE) from glucose monitoring data.

corresponding to their simple arithmetic average seems to work satisfactorily.

Figure 2A shows CGM data obtained from an 8-year-old boy with type 1 diabetes and the smoothed profile. The smoothing does not always capture the full magnitude of some very rapid excursions, and several instances of two or three observations lying beyond the smoothed curve of very narrow peaks and troughs can be observed in Figure 2A, but this is of no consequence—because each true local maximum is identified by searching the original *unsmoothed* observations located in the time interval between the adjacent local minima of the *smoothed* data. Similarly, true local mimina in the unsmoothed observations are found by searching between adjacent maxima in the smoothed profile. The turning points located in this manner are linked by straight lines as shown in Figure 2B.

It will be readily apparent from Figure 2B that many of the turning points located in the above manner define excursions whose magnitudes are less than the specified cutoff criterion. In the next step of the algorithm, the list of all the identified turning points is scanned—and the differences in blood glucose concentration between each turning point and the turning points immediately adjacent on either side are determined. If both differences are less than the cutoff criterion of interest (typically, but not necessarily, 1 SD) then that turning point is marked for deletion. However, a local maximum/minimum blood glucose measurement must be retained, at least temporarily, if it is higher/lower than the

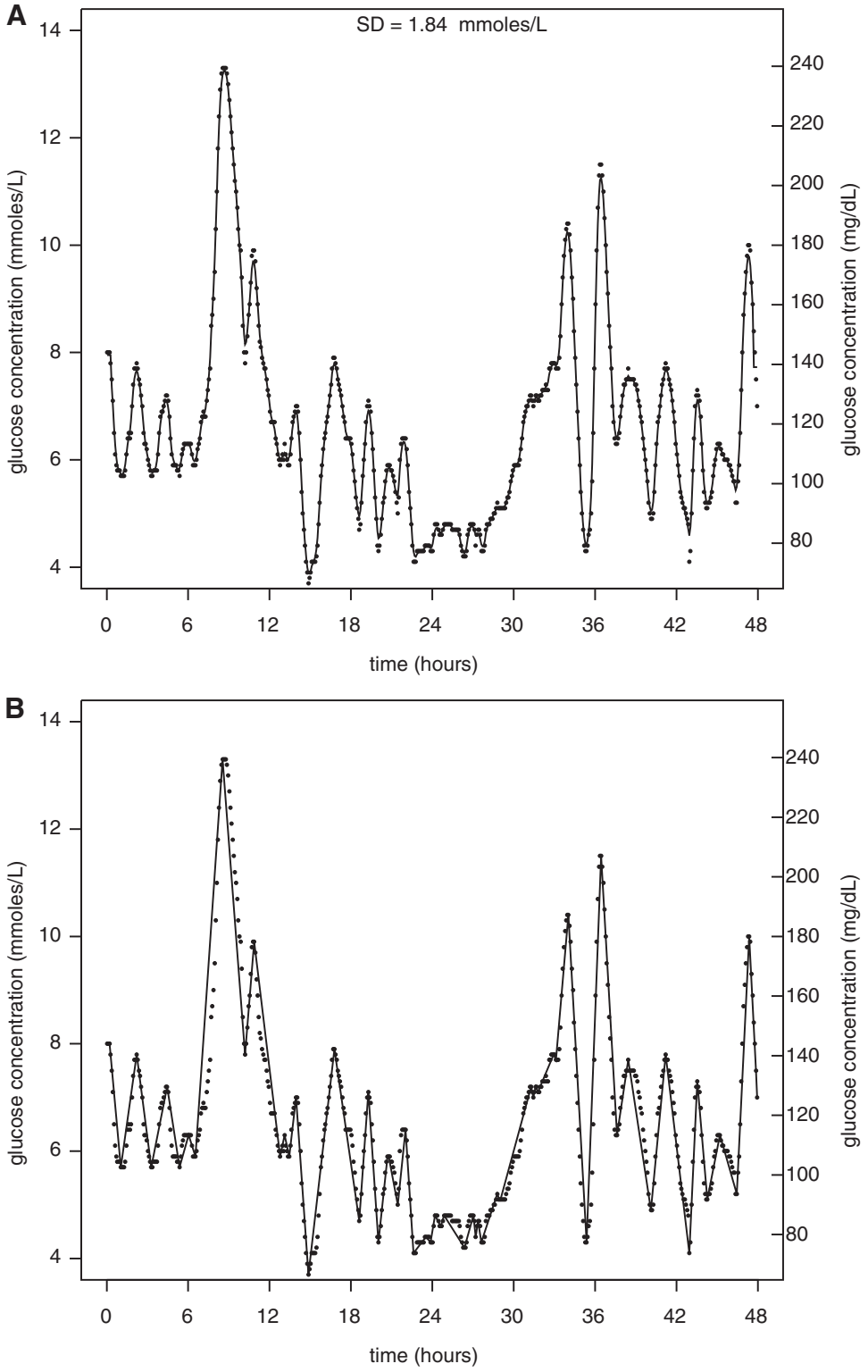

FIG. 2. (**A**) Continuous glucose monitoring data obtained from an 8-year-old boy with type 1 diabetes and smoothed with a nine-point moving average with weights decreasing exponentially either side of the center. The data were collected using a Medtronic Minimed Paradigm® REAL-Time continuous glucose monitoring system (Medtronic, Northridge, CA), with at least four blood glucose levels being measured every 24 h for calibration purposes. (**B**) The continuous glucose monitoring data of (A) with all the identified peaks and nadirs joined by straight lines. (**C**) An intermediate stage in the elimination of small peaks and nadirs demonstrating how some observations cease to be turning points after the elimination of immediate neighbors. (**D**) The final plot after eliminating the insignificant excursions and observations that no longer define turning points in (C). All remaining peaks and nadirs now correspond to countable excursions of 1 SD or more. MAGE, mean amplitude of glycemic excursion.

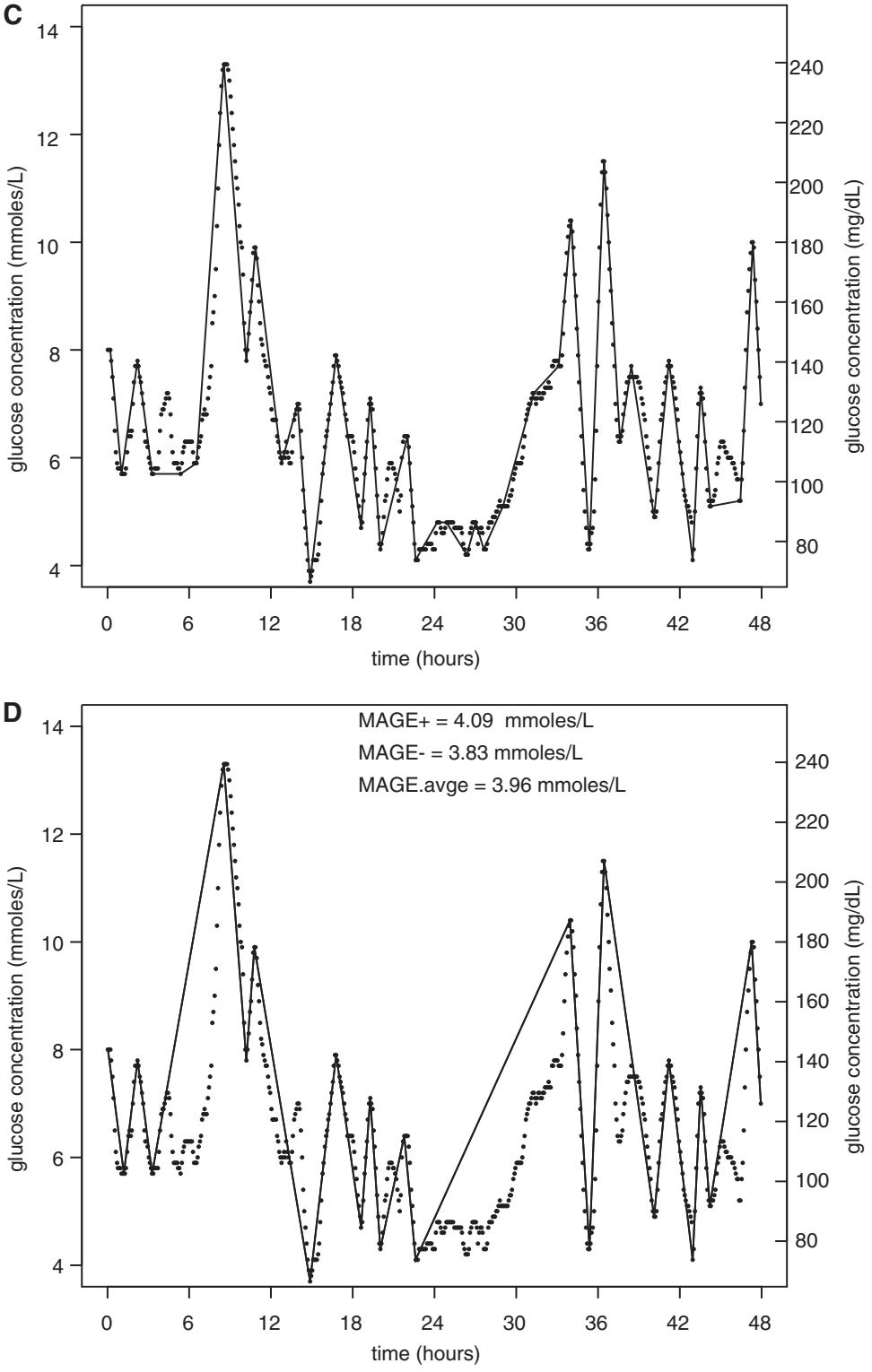

FIG. 2. (*Continued*).

immediate local maximum/minimum on either side, respectively, because it may ultimately define a meaningful excursion if those adjacent turning points are themselves deleted. Similarly, the retention of turning points close to the beginning and end of each dataset that define "cumulative" maxima or minima relative to the first and last data points eliminates some start and end problems that would not arise if the data were embedded inside a larger dataset gathered over a longer monitoring period.

At this stage, some of the retained observations are in fact no longer turning points. Figure 2C shows several such points at 6–7 h, at 29–34 h, and at 46 h. These "false" turning points

are readily identifiable using first differencing again—and they are deleted in the next step of the algorithm. Some insignificant excursions may still have been retained up to this point—so a reiteration of the last two steps just described is often required—and is automatically executed in all cases. With CGM observations spaced 5 min apart, no need for any further iterations has been encountered to date.

It will also be apparent from Figure 2C that some of the remaining turning points identify an excursion of interest on one side, but not on the other (for example, the nadir at around 13 h and the peak around 38 h)—and in a final step these points are identified and deleted, and a final sweep is required to remove any observations that no longer define a turning point.

At this point, the list of turning points required for the final simple MAGE calculation is often complete (Fig. 2D), but a final step eliminates the occasional noncountable excursion persisting at the beginning or end of the CGM profile. The subject in Figure 2D had values for MAGE+ and MAGE− of 4.09 and 3.83 mmol/L, respectively, corresponding to a cutoff criterion of 1 SD = 1.84 mmol/L. To the inexperienced eye, it may seem surprising that the two downward excursions at around 5 and 46 h are not counted, but there is nothing arbitrary about their omission; their magnitudes are less than the qualifying criterion of 1 SD for this subject. Under the rules for calculating a MAGE, the almost biphasic upward excursion between 23 and 34 h also counts as a single, albeit very slow, excursion.

Approach 2: Identification of turning points by elimination

This approach relies on the fact that if three consecutive observations form a (monotone) increasing or decreasing sequence, then the second or middle observation is of no interest, and it can be dropped altogether from the CGM profile. In a first pass with observations spaced 5 min apart, this may result in 80% or more of all observations being eliminated. If the remaining observations are then joined by straight lines, the plot consists of alternating upward/downward excursions similar to those in Figure 2B (but typically including many more minor excursions). The two approaches share the same common algorithm for the subsequent evaluation of the remaining turning points and the elimination of excursions whose amplitudes do not meet the cutoff criterion.

Figure 3 shows a MAGE analysis, using Approach 2, of observations spaced 2 h apart and taken from the same dataset used to generate Figure 2. There are four countable upward excursions exceeding the SD of 1.64 mmol/L and four countable downward excursions, yielding average excursion sizes, MAGE+ and MAGE−, of 3.55 and 3.80 mmol/L, respectively, and an overall pooled average (MAGE.avge) of 3.68 mmol/L. With just 25 data points, Figure 3 illustrates that the algorithm (using Approach 2, without filtering) can also be used to analyze self-monitoring blood glucose data, as well as CGM data. In this instance, the estimate of SD obtained from observations spaced 5 min apart and the estimate of SD based on observations spaced 2 h apart differ by 11%, whereas the averages (MAGE.avge) of MAGE+ and MAGE− for each sampling frequency (3.96 and 3.68 mmol/L, respectively) differ by 7.1%. A much fuller investigation, using the algorithm described here, of how the error of MAGE estimates changes with sampling frequency will be presented elsewhere.

Implementation

The algorithm was developed and implemented using the commercially available software S-PLUS version 8.0 for Windows (S-Plus Statistics and data mining software, TIBCO Software Inc., Palo Alto, CA; www.insightful.com), but with minimal changes the code will run under the academic "freeware" R (R Foundation for Statistical Computing, Vienna, Austria, 2008; www.R-project.org).

Rodbard[5] has pointed out that the original MAGE algorithm as described by Service and colleagues[8–10] does not contain sufficient information for an unambiguous implementation. The use of separately calculated SD values for each day of monitoring poses obvious difficulties if a potentially meaningful excursion occurs over the boundary between day 1 and day 2—and the implementation described here uses a single common SD for the entire period of monitoring. Also, the convention of estimating the amplitude of excursions from either up-swings or down-swings, depending on which comes first, is somewhat arbitrary, and it makes sense in an automated algorithm to calculate both, as well as an overall average of all upward and downward excursions combined. In the author's experience the two estimates, MAGE+ and MAGE−, do not always agree well—especially in subjects with diabetes, for which the correlation was found to be −0.91 ($n = 48$).[4]

The code is contained in a function that takes, as its arguments, a column of elapsed times since monitoring began, a column of the corresponding glucose concentrations, an optional filter; and an identifier for labeling plots.

The choice of smoothing filter in Approach 1 is not critical (for reasons already described), and the user can specify any filter of choice—and it is conceivable that a filter other than the default suggested here may be required for CGM observations that are more closely spaced, say, only 1 min apart. For self-monitoring blood glucose data, which typically consist of much more widely spaced observations, no filtering is necessary—and it should not be used. Several other measures of glycemic variability/control (viz., J-Index, mean of daily differences, continuous overall net glycemic action, and glycemic risk assessment diabetes equation) are calculated at the same time as the MAGE—and the code (including plotting commands) is available free on request from the author.

Calculation of the MAGE by any method (manual or automated) should always be checked visually using plots like Figures 2D and 3. Mistakes made during the manual calculation of the MAGE are rapidly identified and rectified when graphical representations depicting the peaks and nadirs used in both methods of computation are compared. A trained postdoctoral fellow who performed manual estimation of the MAGE from 10 CGM datasets scored perfect agreement in every instance.

The occurrence of multiple small fluctuations near the beginning and end of a CGM dataset posed the most problems in finalizing the current version of the algorithm, which is presented here in the expectation that it may still need to evolve in order to cope with some rare situations, yet to be discovered. A total of 104 datasets had been "analyzed" successfully without manual intervention at the time this article was submitted—and identical results were obtained using the two different approaches (with and without a filter).

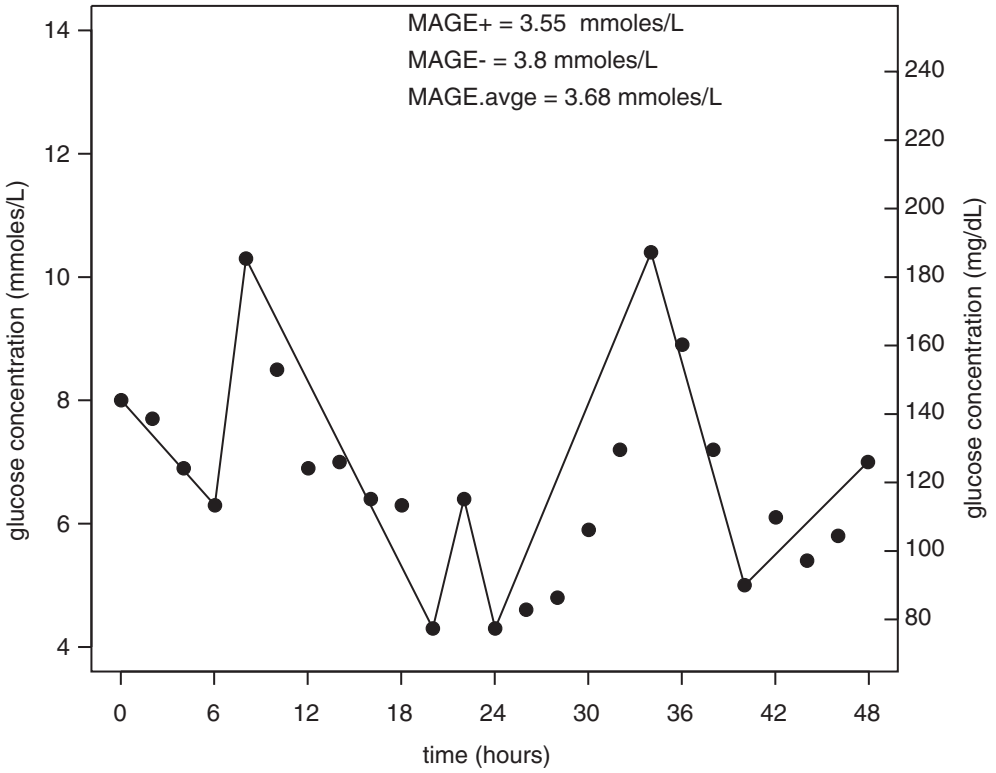

FIG. 3. Mean amplitude of glycemic excursion (MAGE) analysis of blood glucose observations 2 h apart, taken from the same dataset used in Figure 2. This illustrates how the algorithm can also be applied to self-monitoring blood glucose data.

Discussion

As CGM becomes increasingly attractive, the availability of an automated MAGE algorithm such as that described here provides a research tool for examining the properties of this "classic" index of glycemic variability—and it should facilitate a determination of whether MAGE offers any advantage over other indices of glycemic variability in terms of its ability to predict adverse outcomes. We already know that the much more simply calculated SD is very highly correlated to the MAGE in children without diabetes, but less so in 48 children with type 1 diabetes.[4] Rodbard[5] has also noted that the ratio of MAGE to SD in adults with type 1 diabetes is remarkably constant at around 2.45–2.48, and in the 48 pediatric subjects with type 1 diabetes referred to above, this ratio was extremely similar at 2.43 ± 0.04 (although the best-fitting straight-line model also had a small intercept of 2.05 ± 1.35 and a slope of 2.00 ± 0.28).

Several other questions relating to the usefulness of MAGE for assessing glycemic variability will be much easier to address given the availability of this tool:

- Is the most commonly used criterion for defining meaningful excursions (1 SD) the most appropriate?
- Is it really necessary to re-estimate the SD for each day of monitoring?
- Is it even appropriate to define excursions in the relative terms of SD units—or would an absolute criterion like, say, excursions greater than 2 mmol/L be more predictive of complications?
- Are rapid excursions more predictive of adverse outcomes than slow ones, which occur over several hours?
- Does an average (MAGE.avge) of both upward and downward excursions provide a more stable index than just the MAGE+ or MAGE−?
- How frequently must blood glucose concentration be sampled in order to provide reliable estimates of MAGE?

These and other questions will be addressed in future communications.

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Author Disclosure Statement

No competing financial interests exist.

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