Measurement of MAGE (Mean Amplitude of Glycemic Excursion) at Diabetics with Interpolation Method

Heni Hendaryati\textsuperscript{1*}, Askandar Tjokroprawir\textsuperscript{2}, Lailis Syafa'ah\textsuperscript{1}

\textsuperscript{1}Muhammadiyah University of Malang, East Java of Indonesia, lailis_tsd@yahoo.co; heniumm123@gmail.com
\textsuperscript{2}Faculty of Medical, University of Airlangga, East Java of Indonesia, ranchman_syah2002@yahoo.com

\textbf{Abstrak}

Diabetes Millitus is a disease that characterized by glycemic disorders including sustained chronic hyperglycemia and acute glucose fluctuations. MAGE is an important variable to solve clinical problems for patients DM and will generate oxidative stress that contribute to the development of macro and microvascular complications. MAGE is usually used with continuously blood glucose monitoring system using a device called a Continuous Glucose Monitoring (CGM). Due to technical reasons, CGM cannot be done, so the glucose measurement must be done in a discrete (non-continuous) to measure blood sugar seven times a day for 3 days (according to the age sensor). To obtain continuous data, the interpolation technique approach is needed so that the generated of data model are same with the CGM.

\textbf{Keyword:} CGM, diabetics, MAGE, interpolation method.

\textbf{1. Introduction}

Diabetes mellitus (DM) is the most common metabolic disorder or a chronic metabolic disorder with multiple etiologies characterized by high blood sugar levels [1]. Theoretical and preclinical studies demonstrated that glycemic variability is an important parameter that is used to solve a clinical problem in patients with DM. Glycemic variability produces oxidative stress and potentially contribute to the development of macro and microvascular complications [2, 3, 4] especially heart disease coroner. In addition to the three parameters of glycemic control (glucose triad), glycemic variability has an independent risk factor for complications of diabetes.

The Mean Amplitude of Glucose Excursion (MAGE) is glycemic variability. MAGE is usually used with a continuously blood glucose monitoring system using a device called Continuous Glucose Monitoring (CGM). CGM provides a readout of blood glucose levels every 10 min. However, there were published medical studies where MAGE used with a smaller set of data, usually 7–10 readings for 2–3 times per days (aged sensor). For technical reasons, CGM cannot be done then the measurement of glucose in this study conducted in discrete (non-continuous) to measure blood sugar seven times for 3 d. The obtained data measurement is still discrete data, and must be converted into continuous data with a mathematical model interpolation technique approach. Measurement data obtained is still discrete data and must be converted into continuous data with a mathematical model interpolation technique approach.
(ICGM / Interpolated Continue Glucose Monitoring), so that the same data model generated by CGM.

Interpolation is a way to find the value among several data points that have been known to estimate a function, in which that function is not defined by a formula but only by defined the data from the measurement results [5]. Interpolation Polynomial Spline is an Interpolation form that is divided into sub interpolation (piecewise) polynomial. Interpolation polynomial spline is preferred because the interpolation mistakes can be made smaller when using low degree polynomials. Spline interpolation can avoid problems of phenomenon Runge (Runge's phenomenon), in which the oscillation can occur between the point when using a high-degree polynomial interpolation.

Mathematical models in this study conducted by two approaches: Equation-based analytic theory and physical phenomena observed systems, and more empirical equations based on relationship between observed input and output system. Interpolation used in this research is spline interpolation, for a given input fluctuations in high blood sugar degree (oscillation) so used alternatives to get a curve through a number of points by dividing several subintervals, and on each subinterval prepared polynomial interpolation.

2. Material and Methods

Several studies have shown the bad effects from sustained chronic hyperglycemia that results in excessive protein glycation and activates oxidative stress [2]. Role variability glucose (glycemic) is less documented, but the value of the average fluctuation of glucose will activate oxidative stress. So, it is recommended that the treatment strategies for diabetes should be directed to reduce to the minimum of the various components of disglychemic

2.1 Variable Glycemic

Glycemic variability is an important parameter that is used to resolve potential clinical problems in patients with diabetes. It is known that glycemic variability produces oxidative stress and potentially contribute to the development of macro and microvascular complications [3,4]. Currently, the best measurement for assessing glycemic variability is by Mean Amplitude of Glycemic Excursion (MAGE). However, MAGE not in routine clinical use. A routine measurement of glycemic variability clinical cause an important measure of overall glucose control. It predictors to the risk of complications of diabetes that are not detected by glycosylated hemoglobin levels (HbA1c). Good influence also reported by the DCCT (Diabetes Control Complications Trial) and by the UKPDS (United Kingdom Prospective Diabetes Study) 1998: Reduction of microvascular complications contribute to the reduction of glikemic excursi (variable glikemic).

Assessment of glycemic control in diabetic patients should include three parameters, describes as "glucose triad" [3]: hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and postprandial glucose (PPG) as illustrated in Figure 1.
Figure 1. Illustration of three Glycaemia parameters [10]

MAGE is a general size of the volatility of blood glucose levels, a indication level of diabetes control. Mage is usually used with a blood glucose monitoring system continuously (CGM), which provides readings of blood glucose levels every 10 seconds. However, there were published medical studies which uses Mage algorithm by setting the data smaller, typically 7-10 readings per day for 2-3 days [4]. Mage can be calculated by equation-1 [6].

$$\text{MAGE} = \sum_n a_n$$

(1)

There are two aspects that are important in the calculation of MAGE: first, not considering the MAGE excursion significant frequency, just average amplitude. Secondly, not considering the MAGE excursion glycemic which outside the normal range. MAGE only count high average amplitude of glucose that exceed the standard deviation for a particular day (only include the value of the peak to peak on bottom or vice versa) as shown in Figure 2.

Figure 2. Example of MAGE calculation for 24 h with CGM and SD=63 [4]
MAGE in this study are the measured variables of glycemic discrete (discontinuous) since the CGM measurement techniques cannot be done to obtain continuous data required, in engineering approach called as interpolation. Interpolation is the process of discrete data approach into continuous through curve-fitting in a mathematical model equations. Curve fitting is the process of data smoothing.

2.2 Interpolation Methods

Basically, this research was to develop a system through software integrated with existing tools (glucometer). This system can calculate the value of glycemic variability. MAGE is the glycemic variability that can be calculated using this system. MAGE is usually show as continuously blood glucose monitoring system using a tool called CGM (Continuous Glucose Monitoring) as shown in Figure 3.

However, due to technical reasons CGM cannot be done, then the measurement of glucose in this study conducted in discrete (non-continuous) to measure blood sugar as much as seven times a day for 3 d. Obtained data measurement is still in discrete data and must be converted into continuous data interpolation technique approach (ICGM / Interpolated Continue Glucose Monitoring), thus, the generated data model is same as CGM.

![Continuous glucose measurement](image)

**Figure 3.** Continuous glucose measurement [7]

The problem often faced in engineering is to estimate a value between several data points that have been known the value. The method used to estimate this is interpolation. The used of interpolation is polynomial spline since it generated data in high degree (fluctuation). Interpolation polynomial spline is used as the data generated a high degree (fluctuation). The mathematical equation is simultaneous air-order polynomial equation m which:

\[
y = a_0 + a_1 x + a_2 x^2 + ... + a_{m-1} x^{m-1} + a_m x^m \quad \ldots \ldots \quad (1)
\]

By entering into the value of each point above polynomial equations, obtained simultaneous equations with n-equations and n-independent variables then obtain simultaneous equations:
Completion of the above simultaneous equations is \(a_0, a_1, a_2, a_3, \ldots\), an values which is the coefficient values of polynomial functions approach. By entering the \(x\) value of the wanted point at the polynomial function, the value of the \(y\) point is obtained.

Interpolation with polynomials often gives non-acceptable results. Polynomial interpolation resulting from a large number of data points is usually have high degree. Polynomial with high degree usually oscillatory (fluctuations). As a result, the changes of the data in small intervals can lead to large fluctuations in the overall interval. For this reason, the interpolation using a polynomial are having low degree [8]. By limiting the degree of the polynomial, interpolation will get a smooth curve as expected by dividing some point into subintervals. And also on-each subintervals are arranged polynomial interpolation that produces a curve consisting of the top pieces polynomial curve with same degree level. The example of interpolation spline are shown in Figure 4.

![Figure 4. Interpolation Polynomial Spline](image)

Glucose levels on diabetic patients was measured using a glucometer Accu Chek Performa Nano. It consists of a sensor (strip) that functions convert glucose into signals or electrical quantities and displayed on the monitor in the form of numerical data (discrete) that can be stored in a memory integrated with the tool. The data measurement is converted into data continue using polynomial spline interpolation approach with Sintax:
yy = spline(x,Y,xx) => Common forms using cubic spline interpolation to find yy values, the values that underlie function Y from the values of interpolant xx.

pp = spline(x,Y) => the piecewise polynomial dari Spile Cubic.

p = polyfit (x,y,n) => Obtained polynomial coeisienf with vector length n+1 (n=10).

[p,S] = polyfit (x,y,n) => Return the polynomial coeisienf = polyval (p,x) p and structure of S for polyval that use to obtain error prediction.

3. Results and Discussion

The results of this study is a form of discrete data from glucose measurements of diabetic patients taking for 3 days and 7 times per day measurements (before and after breakfast, before and after lunch, before and after dinner and before bedtime) to get the value of MAGE, it required continuous data with change discrete data into continuous data interpolation technique approach. Discrete data measurement results are shown in Figure 4 and the results of continuous data can be seen in Figure 5.

Figure 5. Measurement results of data discrete

On the x-axis: number 1 to 21 are the number of measurements. 1.2 = measurements result of blood sugar before and after 1 hour breakfast on the first day. 3.4 = measurement results of before and after 1 h lunch on the first day. 5.6 = measurement results of before and after 1 hour dinner on the first day, and so on. Y axis: the concentration of glucose.

The measurement results in Figure 5 is the glucose data taken from the first patient blood sugar during the 3 days. It takes 6 times per day so total 18 measurement (on the horizontal line / axis x) which is done manually by using Glucometer Accu Chek, while the vertical line (y-axis) is a blood sugar level (mg / dL). Blood sugar of patient fluctuates and will rise after 1 hour consume food (2nd breakfast measurements, 4th lunch measurements, and the 6th after dinner measurement on the 1st dAY. And number 9, 11 and 13 for d 2 as well as for day 3 which is measurement 16, 17 and 18).
Measurements results of continuous data interpolation Figure 6. Such as discrete data, the horizontal line indicates continuous data presented the taken blood in minute (time) that is 3 d $\times$ 24 h $\times$ 60 min total 4 320 min (x-axis), while the vertical line is the concentration of glucose (y-axis) as well as discrete data. Continuous blood glucose measurement results provide information about the amplitude, frequency and wave pattern of glucose fluctuations, the price of HbA1c (corresponding measurement results Lab.) And at the same time the results of MAGE calculation is based on the value of the blood sugar fluctuations.

Figure 6. Interpolation result of continuous data

Results of continuous measurement of blood sugar (interpolation) provides information on the amplitude, frequency and wave pattern of glucose fluctuations. While the price of HbA1c (corresponding measurement results Lab.) MAGE calculation results based on the value of the blood sugar fluctuations that HbA1c = 14.8 % and MAGE = 90. The yellow line (horizontal) shows hyperglycemic information threshold and the green line shows the hypoglycemic threshold.

To prove that the interpolation a result (changing the discrete data into continuous data) is correct, it needs to be tested by taking a sample of data continuous that returned again into discrete data in Figure 7 is a continuous sample data and Figure 8 is the plotting result of discrete data.
In Figure 8 and 7 seen that there are similarities in the chart thus it can be explained that the results of continuous data after converted into discrete are almost similar. So the technique of interpolation approach in this research can be used to convert discrete data into continuous data.

4. Conclusion

This research presents the continuous glucose fluctuations image using Interpolasi polynomial Spline method. This method can be used to describe the pattern of fluctuations of glucose with discrete / non-continue glucose measurements (Glucose is carried out 7 times a day for 3 d). The
results are a taking blood sugar by using CGM (Continuous Glucose Monitoring) as the development of the glucose measurement techniques that already exist (Glucometer). MAGE (Mean Amplitude of Glycemic Excursion) can be calculated by measuring the discrete of blood sugar (non-continuous) with interpolation technique to obtain continuous values.

5. Reference


