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Expert System for Blood Glucose Fluctuations Measurement Based on MAGE (Mean Amplitude of Glycemic Excursion) and HbA1c On Diabetic Using K-NN (Nearest Neighbor)

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ABSTRACT

Diabetes mellitus (DM) is a kind of disease that is characterized by glycaemic disorder, including chronic hyperglycaemia and fluctuation of glucose level. The fluctuation of glucose level produces excessive protein glycasion and may activate oxidative stress. This condition is the main mechanism that causes secondary diabetes complication. Moreover, there is also a relationship between glycaemic variability and β-cell dysfunction. MAGE (Mean Amplitude of Glycemic Excursion) is a glycaemic variability that is useful to solve clinical problems in patients with diabetes. This study aims to develop the technique of continuous measurement of blood sugar that can describe the pattern of fluctuation with integrated measuring of HbA1c levels and MAGE. MAGE measurements are conducted by the identification and screening of people with diabetes through medical records of glucose continuously, However, in these study measurements of glucose are performed non continuously, to obtain continuous data by interpolation transforming. Data in medical records are then entered to the computer and classified based on MAGE and HbA1c levels according to PERKENI. The classification process is utilizing K-NN (K-Nearest Neighbours) artificial intelligence technology. There are 4 types of fluctuation patterns based on HbA1c (class I HbA1c = 7-8%, class II HbA1c = 8% -9%, class III = 9-10% and class IV HbA1c> 10%) and 3 types of MAGE values (A = Upward/high, N = Average, B = Below/low). The results of this study indicate that there are trends of relationship between HbA1c and MAGE level. The Clustering of glucose fluctuation model using K-NN showed that when the HbA1c level is high, then there is a tendency of high MAGE level and vice versa..

KEYWORDS: Diabetes Mellitus, MAGE, K-NN, Blood Glucose, HbA1c

INTRODUCTION

Diabetes mellitus is a kind of disease that is characterized by glycaemic disorder, including chronic hyperglycaemia and fluctuation of glucose level. The fluctuation of glucose level produces excessive protein glycasion and may activate oxidative stress. This condition is the main mechanism that causes secondary diabetes complication. Moreover, there is also a relationship between glycaemic variability and β-cell dysfunction [1][2].

MAGE (Mean Amplitude of Glycemic Excursion) is a glycemic variability that is useful to solve clinical problems in patients with diabetes in addition to three other parameters of glycemic control (HbA1c, FPG, and PPG). MAGE is considered as the "gold standard" for calculating the glycaemic variability that is calculated by averaging the difference between the peak (maximum) and the bottom (minimum) respectively, where the difference should not be greater than the standard deviation [2]. MAGE should be performed by measuring blood glucose at least 7 times a day for 3 days. The MAGE calculation is done with the equation 1 [3]:

$$\textbf{MAGE} = \sum \frac{\lambda}{x} \qquad \text{…….....1)}$$

Note:

λ = the absolute difference between the maximum and the minimum value of blood glucose

x = the number of observation

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MAGE calculation requires measurements in continuous fashion (CGM/Continuous Glucose Monitoring). Because of handicap, measurement of glucose can be conducted in discontinuous fashion or discretely by interpolated transforming.

Interpolation method is performed by estimating a formula based on a set of data. Interpolation can also be applied to digital image processing, making contours, and is useful in the recovery process where the result is the same with CGM measurements and can be calculated with equation 2 [4].

$$p\ (x) = a_n x^n + a_{n-1} x^{n-1} + ... + a_2 x^2 + a_1 x + a_0 \quad \ldots\ldots 2)$$

Note:

$p(x)$	= polynomial interpolation function
a_n	= polynomial coefficient
x	= the new point of sought value

Epidemiological and intervention studies have recently demonstrated that the occurrence and progression of chronic complications in patients with diabetes are closely related to not only Hion.bA1c level, but also glycaemic variability [5][6], so it is necessary to design strategies to reduce the complications of diabetes by measuring of HbA1c level and glycemic variability (MAGE). Even though, MAGE value is calculated by CGM through the measure of glucose this is still done manually and not integrated with the others (HbA1c and glucose) and not included in routine clinical use [7][8][3][9]. This study creates an Expert System using Artificial Intelligent with K-NN algorithm. K-NN is a method of classifying an object with the nearest Euclidian distance based on learning data [10].

$$d_i = \sqrt{\sum_{i=1}^{p} (x_{2i} - x_{1i})^2} \quad \ldots\ldots\ldots\ldots\ldots\ldots 3)$$

The analysis of patients' data is based on the frequency spectrum (graph) that forms a wave pattern using interpolation method. Then, the results of the spectrum are classified based on the pattern of the shape that is associated with HbA1c measurement based on PERKENI with K-NN algorithm and learning system. This process is resulted an overview of fluctuations level of blood sugar based on HbA1c levels and MAGE value. This calculation can be used by clinicians and people with diabetes to prevent or to slow down further complication.

MATERIALS AND METHODS

This research is a study that explores the theoretical analysis and refers to the pattern of fluctuations of blood glucose that are measured discretely (non continuously) for 3 days, 7 times each day (before and after breakfast, before and after lunch, before and after dinner and before bedtime) using a measuring instrument of Gluco Meter PERFORMA NANO which is produced by ACCU CHEK with the accuracy rate of 99% [13]. Furthermore, the measurement results can be stored in a memory and can be uploaded to a computer for further processing.

This data is in the form of discrete data; to determine the glucose fluctuation model, discrete data should be transformed into continuous data using interpolation approach. Furthermore, using K-NN (K-Nearest Neighbor) algorithm, fluctuation patterns can be classified so that it can describe the pattern of fluctuations of blood sugar level based on HbA1c level and variable glycaemic index (MAGE). Figure 1 shows the diagram of the system in this study.

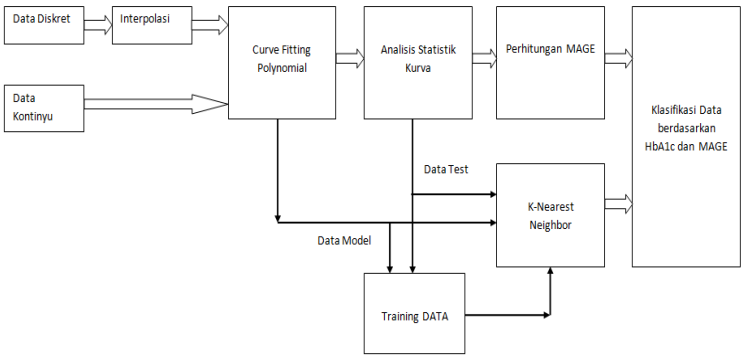

Figure 1. System Diagram

Subject of study

Population and study subjects are subjects that fit the study criteria. The target population in this study was patients with type 2 diabetes mellitus that classified based on HbA1c level according to PERKENI. There are 5 groups of DM, however, in this study only 4 groups are used, they are **class I** HbA1c = 7 % (HbA1c < 7.6), **class II** HbA1c = 8 % (7.5 < HbA1c < 8.6), class **III** HbA1c = 9% (8.5 < HbA1c < 9.6) and **class IV** HbA1 = 10 (HbA1c > 9.6)**.** The patients criteria are:

1. Having a normal Body Mass Index between 18.5 and 25.0 (Optional)
2. Being adult, between 25 and 65 years old
3. Being DM pathological subjects, who have blood glucose levels of ≥ 200 mg/dl after meals, and who have fasting blood glucose levels of ≥ 126 [11].
4. Being approved by doctors for glucose measurement
5. Having HbA1c level of > 7%, where HbA1c examination is conducted on a laboratory NGSP certification.

The number of study subjects are 62 patients which are classified into 4 classes based on HbA1c level. The subjects are also devided as training data and test data.

Signal processing using K-NN

` Data stored in the instrument memory is inserted into a computer and processed into continuous signal in the following stages:

- Signal Processing
  - Converting XLS files in the form of discrete data into a CSV file of data minutes versus glucose levels
  - Transforming CSV data into continuous data with interpolated method
  - Calculating MAGE using equation 1
- Algorithm K-NN
  - Defining the K parameters (Max Value, Min, Threshold Value and norm of residual Value)
  - Calculating the Euclidian distance with equation 3
  - Predicting calculated value of distance query
  - Clustering and descripting the pattern of fluctuations in blood glucose levels and HbA1c levels based on glycaemic variable index (MAGE) [9]*:* ***Upward Excursion (A/Above (Unstable . >85mg/ml) MAGE.avge: Average Excursion (N/Normal/stable/range*** **67 to 82** mg./100 ml*) and MAGE : Downward Excursion (B / Below / Normal /* range, 22 to 60 mg./100 ml*).*
  - Creating of Data Base, all of data result are presented in this data base

RESULTS AND DISCUSSION

Identification and screening of people with diabetes through medical records and random glucose measurements are for subjects who have blood sugar higher than normal level (> 200 mg / dl) and HbAc1 levels> = 6.5%.

In this study there are two data Sweden (continuous)[12] and Indonesian (discrete data). For Sweden the data is used to see patterns and fluctuations as the initial model. While the Indonesian data uses interpolation methods to generate continuous data, and then calculate based on the value of HbA1c, MAGE, and curve fitting and in every calculation is grouping performed by class and group data base (I-A, I-N, I-B; , II-A, II-N, II-B; ... IV-A , IV-N, IV-B). the data grouping presented in the form of a database such as image 2

There are two dataset that used in this study, the Sweden dataset which is continuous and the Indonesian dataset which is discreet. The Sweden dataset is used as a base to build initial model and fluctuation pattern while the Indonesian dataset is used with interpolation method in order to produce continuous data, and then calculated HbA1c value, MAGE, curve fitting. Each calculation is conducted to grouping the data into group (I-A, I-B, I-N; II-A, II-N, II-B; ... IV-A, IV-N, IV-B). The results of the grouping is stored in database such as figure 2.

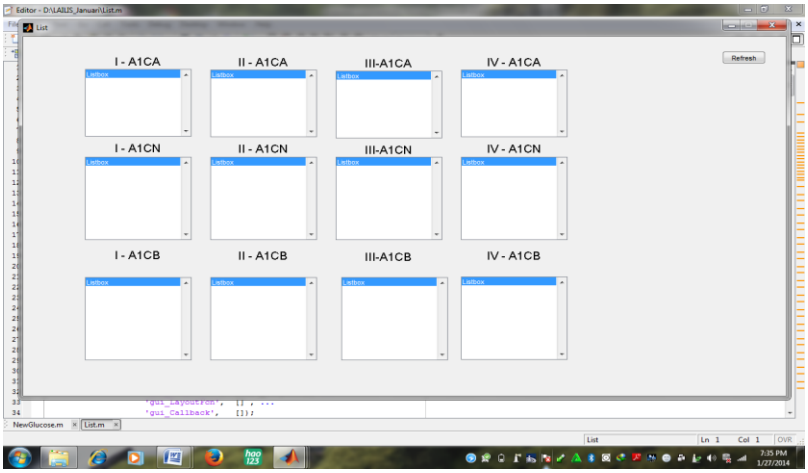

Figure 2. Grouping result in the database

In the picture above, the grouped data is empty because no data is entered, but already there is already a classification based on HbA1c value and MAGE.

The classification of Glucose Fluctuation Pattern Based on HbA1c and MAGE

The data that is grouped based on glucose level become the input of the K-NN. Each HbA1c and MAGE calculation is followed by data classification and statistical analysis resulting max, min, mean and norm of residual parameters. Norm of residual is obtained from the proximity distance between curve fitting graph to the original data/interpolate results and indicate the level of fluctuation of original curve/interpolation results. The higher the Curve volatility level, the higher the norm of residual.

RESULT

The results of this study are patterns that are classified into:

- 4 classes based on HbA1c value (PERKENI)
  - ✓ **class I** HbA1c = 7 % (HbA1c < 7.6),
  - ✓ **class II** HbA1c = 8 % (7.6 < HbA1c < 8.6),
  - ✓ **class III** HbA1c = 9% (8.5 < HbA1c < 9.6)
  - ✓ **class IV** HbA1 = 10 (HbA1c > 9.6)**.**
- 3 classes based on MAGE value
  - ✓ A (Above/Unstable) > = 86 mg/dl
  - ✓ N (Normal) between 62 mg/dl and 85 mg/dl
  - ✓ B (Below) < = 62 mg/dl

When the patient data is selected randomly as the input data, the data will be stored in the database based on HbA1c and MAGE values automatically.

- The measurement of patient 1

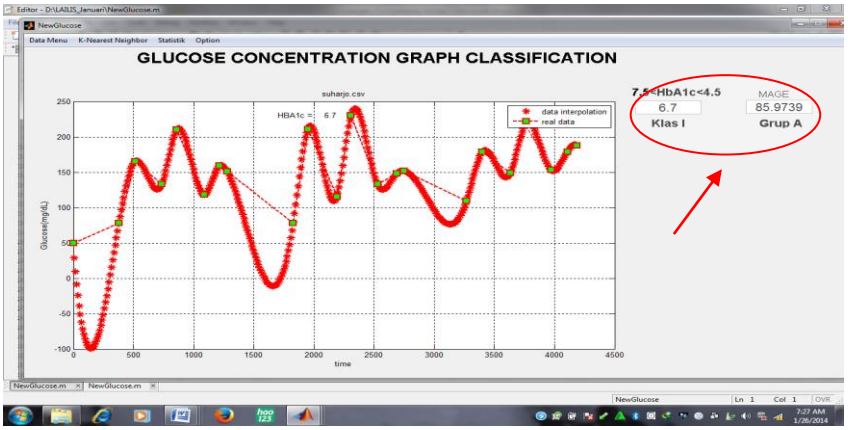

Figure 3 Fluctuation pattern of patient 1

Figure 3 show that patient 1 has HbA1c = 6.7% which is included in class I and MAGE = 85 mg/100 ml (arrow sign) which is included in class A (above). So the final class is I-A. The data of patient 1 is stored in the database as shown in figure 4.

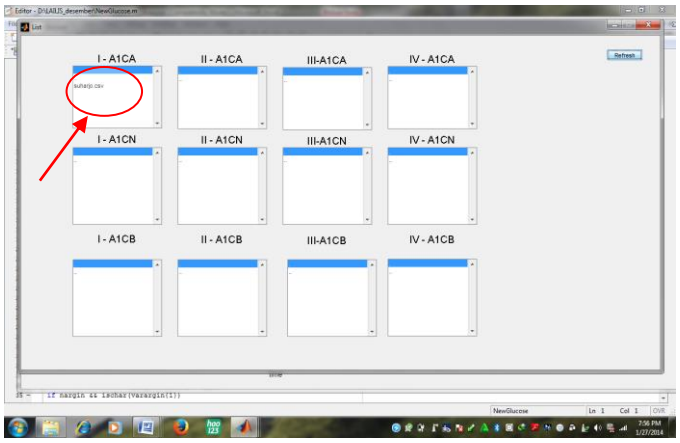

Figure 4 the classification of patient 1 follows the criteria into database

In figure 4, patient 1 is already stored based on HbA1c level and MAGE value (sign arrow)

- The measurement of patient 2

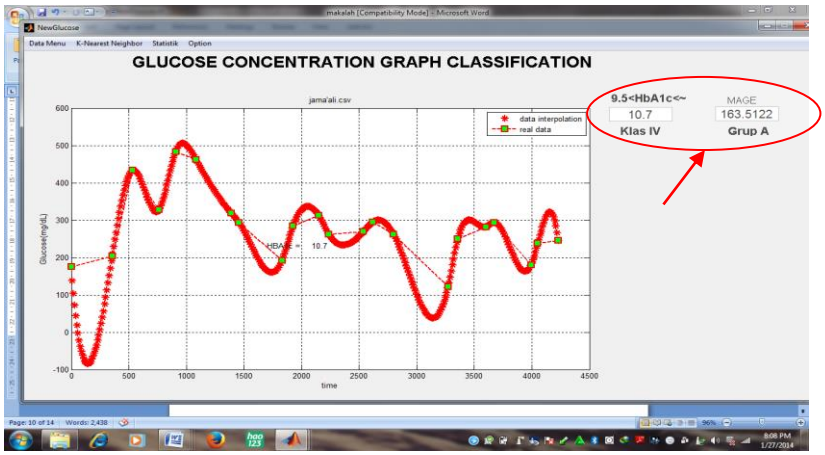

Figure 5 Fluctuation patterns of patient 2

Figure 5 show that patient 2 has HbA1c= 10.7% which is included in class IV and MAGE = 163.5 mg/100ml (arrow sign) which is included in class A (above). The stored data of patient 2 in the database is shown in figure 6.

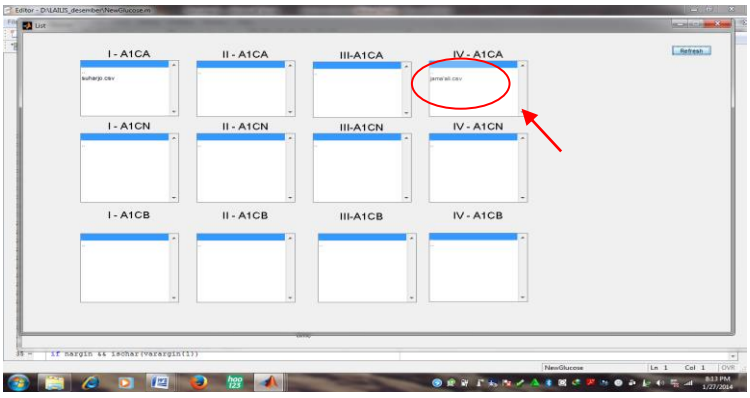

Figure 6 the classification of patient 2 follows the criteria into database

For all of the 62 patients, the database is shown by figure 7.

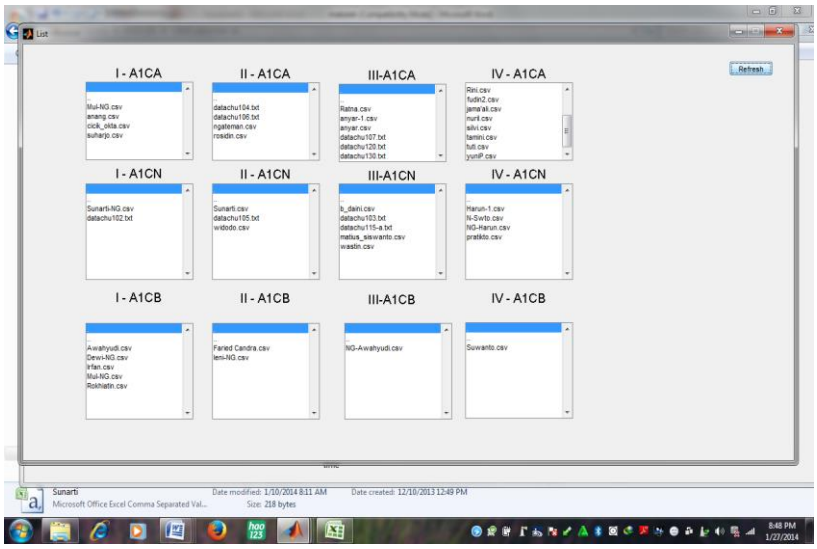

Figure 7. The database of patients' classification follows the criteria

The results of classification are described using bar chart as figure 8.

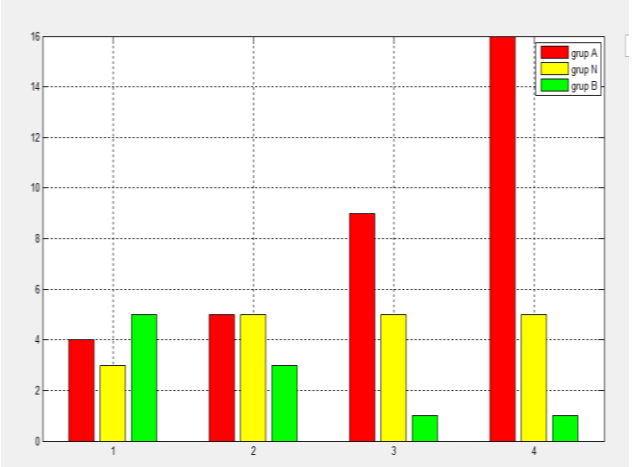

Figure 8. Bar chart of all 62 patients

The red colour in the Figure 8 indicates MAGE group A (high/above), while the yellow bar shows group N (stable) and the green colour reports low/below MAGE (group B). Furthermore, X-axis is described as HbA1c classification which is graded from I to IV. From Figure 8, it can be concluded that the level of MAGE in the fourth range (group of high HbA1c) has high number of diabetics who have high MAGE, 76% (A). In this range, the number of diabetics who are in the stable MAGE is about 20% and it has lower MAGE (B), 4%, in this range.

Moreover, in range I (low HbA1c group), the number of diabetic who have high MAGE is 20% (A), the number of diabetic in the stable MAGE (N) is 33,3% and the number of diabetic in the low MAGE (B) is 47.7%. In summary, the number of diabetic in the high MAGE (A) is common on the fourth range (high HbA1c), However, the number of diabetic with low MAGE is common in the first range (low HbA1c).

CONCLUSION

1. K-NN algorithm can be implemented in the field of medicine that helps to classify the Diabetes Mellitus desease by measuring the fluctuation of blood sugar discreetely.
2. Discreet glucose measurement (in 3 days, 7 times in each day) can describe glucose fluctuation pattern use interpolation method utilizing CGM (Continuous Glucose Monitoring) technique.

3. MAGE (Mean Amplitude of Glycemic Excursion) can be calculated by measuring discrete value with interpolation techniques.
4. With continuous measurement of blood glucose, the fluctuation patterns can be grouped by HbA1c levels follows based on PERKENI (there are 4 classes, I -> HbA1c = 7 %, II -> HbA1c = 8%, III -> HbA1c = 9 and IV -> HbA1c = 10 %) MAGE values (there are 3 groups A (Above), N (Average) and B (Below)), utilizing K-NN algorithm.
5. The fluctuated glucose value may increase value.
6. There is a tendency that HbA1c level is correlated with MAGE value, HbA1c level is proportional to the MAGE value.
7. DM patients with stable control tend to decrease the value of MAGE

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