A NOVEL APPROACH TO ESTIMATE VARIATIONS OF BLOOD GLUCOSE USING NONINVASIVE METABOLIC MEASUREMENTS

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ABSTRACT
A novel method has been designed to estimate blood glucose variations noninvasively. The concept of this method is based on the glucose metabolic process in the human body. The data acquisition phase was implemented by measuring metabolic parameters including heat dissipation by conduction at the fingertip, percentage oxygen content of expired air and minute volume of expired air. A data analysis phase was performed to convert the measured parameters to variations of features, which would become input of the calibrated classification model for estimation of blood glucose variations. The classification model can be a 2-class to 5-class system showing different resolutions for the extents of blood glucose variations. In the experimental trial, a total of 190 data points were obtained from 31 normal and 159 type 2 diabetic subjects. The classification accuracy for a 3-class system was 84.26% using a linear discriminant classifier. Multiple regression analysis was also performed to compare the noninvasive method with variations of glucometer readings. The correlation coefficient was 0.88. Preliminary results show that this method has the potential to be used as blood glucose variation monitors and lifestyle educating devices for normal, pre-diabetic and type 2 diabetic persons.

KEY WORDS
Blood glucose variations, heat dissipation, resting metabolic rate, and classification model

1. Introduction
Frequent self-monitoring of blood glucose (SMBG) is crucial for diabetic patients to prevent complications of diabetes [1],[2]. In addition, it was found that lifestyle intervention including behaviour modification plays a significantly important role not only to control blood glucose levels for diabetic patients, but also to prevent or delay the development of diabetes for normal and pre-diabetic persons [3]-[5]. Since SMBG can be treated as a type of behavioural lifestyle intervention, diabetic patients and pre-diabetic subjects should be educated to perform SMBG several times per day in order to provide a better control for each of their blood glucose concentrations. However, most of them are reluctant to implement SMBG using the traditional invasive fingerstick testing mainly because of pain and infection concerns. Therefore, our goal is to develop a noninvasive method that can estimate blood glucose variations in normal, pre-diabetic and type 2 diabetic persons.

Cho et al. has proposed the metabolic heat conformation (MHC) method for noninvasive blood glucose measurement [6]-[10]. This method makes use of thermal and optical techniques to measure body glucose metabolic effects at an extremity, such as a forefinger. A multiple linear regression equation was formed based on the measured parameters. The apparatus was designed by hard-coding the regression equation into a ROM unit using the measured results of only 8 subjects (2 normal and 6 diabetic). The population of sample subjects is too small so that different offsets of the measured parameters due to unique body properties among subjects were not indicated. Thus, the results are far from being conclusive to build an accurate predictive model from the measured parameters.

Instead of measuring a single value of blood glucose level, we describe a novel noninvasive method, which is unique in a way that only the extents of blood glucose variations are computed. Using classification techniques, this method can present the results in a simple, but meaningful manner.

The principles underlying our method are based on the concept of metabolic glucose oxidation. The amount of glucose in blood directly affects the glucose oxidation rate. Studies have shown that hyperglycemia would significantly increase the carbohydrate oxidation (CHO) rate in normal and type 2 diabetic human beings [11]-[13]. Since glucose oxidation is an exothermic chemical reaction [14], heat energy is produced and thus dissipated from the human body. This could probably explain the experimental results previously obtained by Hillson et al. indicating that facial and sublingual temperature increased after intravenous glucose injection in diabetic subjects [15]. Also, Rousselle et al. demonstrated that human energy expenditure would increase after oral glucose load [16]. Resting metabolic rate (RMR) was computed as an index to indicate energy expenditure. To summarize, our method was derived from the findings that blood glucose has an interrelationship between body heat production and
energy expenditure as shown in Figure 1. Thus, it was expected both variations of body heat dissipation and RMR could reflect blood glucose variations.

![Figure 1 – Summary of the findings illustrating a rise in blood glucose consequently increases heat dissipation and resting metabolic rate](image)

2. Research Design and Methods

2.1 Noninvasive measurement technology

The method assumes that body heat production is directly correlated with body heat dissipation. Body heat production was obtained by measuring the amount of conduction heat loss at the extremity (e.g. forefinger). A sensitive heat flow sensor (Data Harvest EasySense) consisting of 400 thermocouples was adopted. The sensor was able to take account on ambient temperature and measure the amount of heat dissipated from the measuring site to the environment by conduction. Heat dissipation from the fingertip was measured and then averaged over 8 seconds.

RMR is a measurement of energy expenditure of human body. It can be calculated using the revised Weir equation, which was derived from previous experimental data of glucose oxidation [17],[18]. By making the assumptions that respiratory quotient equals 1, percentage of total calories due to protein oxidation equals 12.5% and percentage of inspired oxygen equals 20.93%, the simplified version of the revised Weir equation was expressed as:

\[
RMR = (1.039 - 0.05O_2)V
\]  

(1)

O_2 is percentage oxygen content of expired air, and V is minute volume of expired air. A portable oxygen analyzer (Teledyne AX300) and a spirometer (Vitalograph Micro) were adopted to measure O_2 and V respectively from a regular expired breath at the mouth cavity. For calibration and reference purposes, the traditional fingerstick testing method (Medisense Optium Xceed) was also adopted to measure blood glucose level.

2.2 Experimental protocol

The experimental trial was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster at Queen Mary Hospital, Hong Kong. Each volunteer had read and signed an informed consent form before the experiment. A total of 190 Chinese volunteers, aged from 23 to 86, participated in this trial. 31 of them were normal and 159 had type 2 diabetic. Among the normal volunteers, 7 of them were male and 24 were female, while among the type 2 diabetic volunteers, 97 of them were male and 62 were female.

The trial protocol for each subject was designed and described as follows:

1. Subject should report to the clinic fasting (at least 12 hours, no food or drink except water), having not taken his/her morning study medication dose.
2. Subject should sit down and rest for at least 15 minutes before measurements.
3. Subject should have blood glucose measurement taken as usual.
4. Subject should have heat dissipation by conduction measurement taken.
5. Subject should have percentage oxygen content of expired air measurement taken.
6. Subject should have minute volume of expired air measurement taken.
7. Diabetic subject may need to take his/her medication dose depending on the seriousness of his/her condition.
8. Subject should complete eating a meal (standard meal is not necessary).
9. Step 3 to 6 should be repeated 45 minutes after the start of the meal.

2.3 Data analysis methods

In order to construct a classification model, calibration process was performed using the measured parameters. Figure 2 shows the steps of the calibration process. After the raw metabolic parameters and blood glucose level were measured, the metabolic parameters (i.e. amount of heat dissipation by conduction, O_2 and V ) were converted to metabolic features (i.e. average heat dissipation by conduction and RMR ). For each subject, blood glucose variation and variations of metabolic features were computed by subtraction between the values obtained from the first and second measurements. The variations of metabolic features were tested for feasibility to become inputs of the classification model. This test was done by means of multiple linear regression analysis with least-squares method [19]. The feasible variations of features and the corresponding reference blood glucose
variations were used to train and develop a classification model for future estimation of blood glucose variations [20].

3. Results

The variation of average heat dissipation by conduction and the variation of $RMR$ for each of the 190 subjects were computed from the acquired raw metabolic parameters and plotted against blood glucose variation as shown in Figure 4 and Figure 5 respectively. The former plot obtained a correlation coefficient of 0.85, while the latter one obtained a correlation coefficient of 0.70. It could be seen that each of the variations of metabolic features had a primary linear relationship with the corresponding blood glucose variation.

Figure 2 – Steps of the calibration process

Figure 3 describes the steps of the estimating process of blood glucose variations after the classification model was developed. Similar to the calibration process, the raw metabolic parameters were measured and converted to metabolic features. Afterwards, variations of metabolic features were computed and input into the trained classification model. After classification, the extents of blood glucose variations were output in terms of 2 to 5 classes providing different resolutions for the results.

Figure 3 – Steps of the estimating process of blood glucose variations

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Figure 4 – Scatter plot ($R = 0.85$) showing a primary linear relationship between variation of average heat dissipation by conduction (in $W/m^2$) and blood glucose variation (in mg/dl)

Figure 5 – Scatter plot ($R = 0.70$) showing a primary linear relationship between variation of $RMR$ (in kcal/min) and blood glucose variation (in mg/dl)

Figure 6 – Scatter plot ($R = 0.88$) of estimated blood glucose variation (in mg/dl) computed by the two variations of metabolic features versus reference blood glucose variation (in mg/dl) by multiple linear regression analysis
Multiple linear regression analysis with least-squares method was performed to test the feasibility of using variations of average heat dissipation by conduction and \( RMR \) as variations of features input into the classification model. The variations of blood glucose level obtained by the fingerstick testing method were taken as reference to compare with those estimated by variations of metabolic features. The regression result using 190 data points was plotted in Figure 6. The correlation coefficient was 0.88 and the mean absolute error was 15.15 mg/dl. Clarke error grid analysis [21] was not performed since the grid was not designed to analyze variations and thus, the extents of variations.

Regression results demonstrated the feasibility of the proposed variations of metabolic features. Thus, the two features’ variations were input into a developed classification model. The same 190 data points were used and 6 different commonly used classifiers were tested under Matlab environment using PRTools toolbox [22]. The training and testing steps were carried out as follows:

1. 95 data points (i.e. 50%) were randomly selected to train a classifier.
2. The rest of the data points (i.e. 50%) were used to test the classifier.
3. Step 1 and 2 were repeated 100 times to obtain the average classification accuracy.

![Classification accuracies obtained by the 6 classifiers](image)

Figure 7 – Classification accuracies obtained by the 6 classifiers

4. Discussion

Our method emphasizes the analysis of blood glucose variations rather than merely blood glucose values because of two reasons. First, analyzing the extents of blood glucose variations is more meaningful for SMBG purpose. The patients only need to realize how serious their blood glucose concentrations vary without knowing their actual blood glucose levels. Second, even at the same blood glucose level, subjects may possess different sets of metabolic offset values from one another since their biological properties (e.g. skin thickness) are not the same. Hence, if variations were not considered, the results would be affected by the offset values of the individuals. To demonstrate the effects of subjects’ variations, 380 sample points were obtained before computing variations and adopted to investigate the relationship between blood glucose level and metabolic features. The correlation coefficient for the correlation between average heat dissipation by conduction and blood glucose level was 0.32, while for the correlation between \( RMR \) and blood glucose level, the correlation coefficient was 0.15. Multiple linear regression analysis was also performed to test the feasibility of using average heat dissipation by conduction and \( RMR \) as features input into the classification model. A low correlation coefficient of 0.35 and a large mean absolute error of 209.00 mg/dl were obtained. The regression scatter plot was shown in Figure 9. By using a linear discriminant classifier, the corresponding classification accuracy was only 33.11%, 33.68% and 29.14% for 3, 4 and 5 classes respectively. When a 5-class model is adopted, class 1 to 5 will represent “Large Drop”, “Small Drop”, “No Significant Change”, “Small Rise” and “Large Rise” respectively. Nevertheless, for normal, pre-diabetic persons and type 2 diabetic patients without drug or insulin therapy, a 3-class
model may be sufficient indicating only the increase of blood glucose (i.e. “No Significant Change”, “Small Rise” and “Large Rise”) provided that calibration is performed in the morning before breakfast. It is expected that the calibration frequency for our method should be 1 to 2 times per week as the metabolic offset values of an individual do not vary much within a short period of time.

Our method assumes that under resting condition and in the absence of other artifacts, the classification model is able to output the extent of blood glucose variation of an individual correctly. Artifacts include doing exercise, washing hands and touching hot or cold objects. Individuals should avoid artifacts for at least 15 minutes before measurements to obtain more accurate results. Furthermore, individuals having heat related disease (e.g. fever) and respiratory disease (e.g. pneumonia) might cause significant errors to the metabolic measurements. These preventions were implemented in the experimental trial.

The introduction of classification on the extents of blood glucose variations has the advantage of providing a certain tolerance for errors. The classifier can probably tolerate some minor artifacts and fluctuations of metabolic values on account of circadian rhythms of temperature at the extremities and respiratory oxygen consumption [23]. Therefore, unlike the MHC method relying on a multiple linear regression equation, our method predicts blood glucose variations in a fuzzy and representative approach.

It could be observed from the results that variation of average heat dissipation by conduction had a better linear relationship than variation of \( RMR \) with blood glucose variation. This was probably due to the experimental constraint that two breaths were required to measure \( O_2 \) and \( V \). If the two breaths were inconsistent, the \( RMR \) calculated by equation (1) should be less accurate. Thus, improvement of the devices would be made in future study. However, it is still worthwhile to include variation of \( RMR \) as input of the classification model. Regression analysis using the two variations of metabolic features obtained a higher correlation coefficient than those obtained from both of the primary relationships.

Figure 6 indicates another experimental constraint such that sample points were sparsely distributed in the extreme regions. This would affect the classification accuracy of our method. In particular, when a large number of classes, say 5 classes were adopted, the more extreme classes (i.e. class 1 and 5) were not well-trained owing to insufficient points falling into those regions. However, such problem could be solved by performing more comprehensive trials on the extreme cases.

Lastly, it has to be emphasized that fingerstick testing should still be adopted for clinical measurements since accuracy is highly desirable for diagnostic purpose. SMBG measurements, on the other hand, should focus on simplicity so long as results with reasonable accuracy could be obtained because complexity would cause reluctance.

5. Conclusion

Study results show that our method is reasonably accurate to estimate blood glucose variations. The scatter plot of multiple linear regression analysis indicates that variations of average amount of heat dissipation by conduction and \( RMR \) have a linear relationship with blood glucose variation. They are appropriate to become variations of metabolic features for training and testing the classification model. Linear discriminant classifier should be adopted as the classification model to obtain the best classification accuracy out of the other 5 classifiers for the estimation of blood glucose variations. Therefore, our method has the potential to become a device that can monitor blood glucose variations and improve the behavioural lifestyle for normal, pre-diabetic and type 2 diabetic persons.

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References


