Paper

Proposal of prediction accuracy improvement in non-invasive blood glucose measurement using MHC method

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Abstract: According to the World Health Organization, 422 million adults worldwide have diabetes. Diabetic patients must regularly measure and manage their blood glucose levels. However, existing blood glucose meters require needles to draw blood, causing pain and infection problems. The measuring instrument to solve this problem would be a non-invasive blood glucose measuring instrument, but none is practically used at present. The authors have been studying non-invasive blood glucose measurement methods to reduce the burden on diabetic patients. As a result of previous research, we developed a simple non-invasive blood glucose meter and a blood glucose control system. Currently, our aim is to improve accuracy of blood glucose level prediction. In this paper we report on the blood glucose level prediction technique realized by using biological information. As a result, heart rate and MHC method are used as input data, and prediction using machine learning can be performed with high accuracy.

Keywords: blood glucose, non-invasive, MHC,

1. Introduction

Diabetes is one of the top 10 causes of death in the world. The WHO reported that 422 million adults worldwide have diabetes [1]. The number of diabetics in Japan in 2014 was 3,166,000, an increase of 466,000 from three years before. In addition, as shown in Fig. 1, the number of people strongly suspected of having diabetes has been increasing since 1997 [2], and it is predicted that the number of patients with diabetes will continue to rise in the future. The treatment of patients with diabetes aims to prevent development and aggravation of complications characteristic to diabetes and accompanying diabetes, and to maintain the same quality of life as of healthy people [3]. In the management of diabetes mellitus, the blood glucose level must be monitored continuously.

Currently, self-monitoring blood glucose meters that can measure blood glucose levels at home are on the market. By using such a device, the blood glucose level can be repeatedly checked. However, current blood glucose self-monitoring devices acquire a blood sample from the fingertip with a needle and measure it. This causes various problems [4]. A blood sample is obtained with a needle, which is painful and stressful to the patient. Also, needles and test strips are disposable, so they cost money and can cause infections during the blood collection. In addition, when continuous blood glucose measurement is performed in the management of diabetes mellitus, inflammation may

Figure 1: Trends in people suspected of being strongly susceptible to diabetes [2].

occur in the blood sampling area because blood glucose measurement is required several times a day depending on the severity. To solve these problems, minimally invasive blood glucose meters have been developed. For example, a FreeStyle Libre, developed by Abbott Diabetes Care Inc. USA is available. However, the false-positive rate of hypoglycemia remains high [5]. Although it is minimally invasive, the use of needles does not solve the problems of pain and infection. In order to completely solve these problems, there is a need for an inexpensive measuring instrument that does not require needle replacement or test paper exchange for each measurement, that can be easily used at home, and does not require blood sampling, thus not causing any sanitary problems. Such a measuring instrument is called a non-invasive blood glucose measuring instrument, however, none is practically used at present.

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Table 1: Comparison of noninvasive blood glucose measurement methods [12] [13].

Method	Optical method	MHC technology	Smart lens(Google)
Invasiveness	Noninvasive	Noninvasive	Noninvasive
Measurement object	Blood glucose	Metabolic heat	Glucose
Measurement accuracy	High	Low	Low
Medical waste	None	None	None
Production state	Production of prototype	Difficult as medical equipment	Failure
Size	20×10×5cm	Hand size	Contact lens

The importance of glycemic control not only in patients with diabetes but also in medical facilities is attracting attention. In Berghe *et al.* study [6], controlling blood glucose levels to 80~110 mg/dL in patients in intensive care units (ICU) reduced mortality from 8.0% to 4.6%. It was also confirmed that the reduction of complications was achieved. In addition, the American Society of Intensive Care states that it is desirable to control blood glucose levels below 150 mg/dL as a treatment policy for sepsis and shock associated with sepsis [7]. Thus, awareness of the importance of glycemic control in ICUs has increased and has been discussed in related societies. In recent years, with the modernization of hospitals, IOT has been used for e-health, telemedicine, human care, and patient monitoring health services [8]~[11]. However, there is currently no adequate blood glucose monitoring system, and blood glucose levels are measured every few hours in clinical settings. It takes a lot of time and effort including prevention of infectious diseases during the blood collection. Providing a blood glucose meter and a control system that can operate non-invasively and continuously, would be a great medical advance.

The theory of noninvasive blood glucose measurement has been studied for many years. Table 1 compares non-invasive glucose monitoring methods [12] [13]. Previous studies have attempted to measure blood glucose using optical methods [14] or temperature methods [15]. In the case of optical methods, the size of apparatus is $20 \times 10 \times 5$ cm without including the power supply. On the other hand, if a method using temperature is used, it is possible to develop a small measuring instrument that can be mounted on a wearable terminal. This method, called Metabolic Heat Conformation (MHC), is based on the correlation between glucose concentration in the body and the amount of heat released by the body [15].

In this research, we aim to develop a non-invasive blood glucose meter and blood glucose management system that can be used at home. Conventional MHC theory uses blood flow to compensate for predictive values [15]. However, measuring blood flow velocity requires expensive, large instruments. That is, to measure blood glucose levels at home, prediction methods that do not require correction by blood flow velocity are required. As a result of previous research, we developed a simple non-invasive blood glucose meter and a blood glucose control system [16]. A prediction model was also studied to improve measurement accuracy [17]. However, previous studies have found that the predic-

tion accuracy of MHC method is poor. In this study, our goal is to achieve more accurate glucose level prediction by improving prediction methods and predicting blood glucose levels with consideration of biological information. In this paper, we report the results of a study on the prediction of blood glucose levels by considering multiple parameters of the human body in consideration of individual differences in biological responses. We also introduce new parameters that have not been used in MHC theory.

2. Theory

According to a previous study by Stephcnie *et al.* [15], the appropriate sites for noninvasive glucose monitoring are the skin, forearm, wrist, earlobe, and fingertips. The parameters required for MHC method are heat radiation and heat convection. Heat radiation can be calculated by Stefan Boltzmann's law and is determined as Eq. 1.

$$hr = \rho \times \sigma \times (Ts^4 - To^4) \quad (1)$$

$hr (W/m^2)$: radiation

ρ : reflectivity of the skin's surface

σ : Stefan Boltzmann constant

$Ts (^{\circ}C)$: measured surface temperature

$To (^{\circ}C)$: measured ambient temperature

The thermal convection is obtained as Eq. 2.

$$hc = h \times (Ts - To) \quad (2)$$

$hc (W/m^2)$: thermal convection

h : convection coefficient

The equation for calculating the blood glucose level was derived by linear regression analysis based on the Eq. 1 and Eq. 2, and the blood glucose level was measured by an existing blood glucose meter. As an example, the following is the result of deriving the prediction equation. The data used in linear regression analysis are recorded blood glucose levels and fingertip temperature of an adult male at the ambient temperature of $28^{\circ}C$. The sample size is 8 measurements. As a result, the calculation formula of blood glucose level was derived as Eq. 3.

$$\begin{aligned} &\text{Glucose Level (mg/dL)} \\ &= 193.17 + hr + (-96.3) + hc \times 121.9 \end{aligned} \quad (3)$$

MHC method is based on the correlation between glucose concentration in the body and the amount of heat released by the body. In a previous study by Stephcnie *et al.* [15], the correlation between the glucose concentration and the amount of heat released by the body was 0.925.

Figure 2: System configuration.

Table 2: Outline of the experiment data.

Experiment Number	Duration	Number of Subjects	Number of Samples	Remarks
A	12/2017~6/2018	76	136	-
B	11/2018	116	116	-
C	3/2019	59	73	-
D	11/2020	1	18	before and after meals

3. System Configuration

The purpose of the proposed system is to measure blood glucose level and control blood glucose level easily even at home. Figure 2 shows the system configuration. It is mainly divided into a non-invasive blood glucose meter to measure the blood glucose levels and a smartphone application to manage the blood glucose levels. The details are explained in previous studies [16], and are therefore omitted here.

4. Study of Blood Glucose Level Prediction Method

In this study, the measurement experiments using a non-invasive blood glucose meter, accuracy evaluation, and blood glucose prediction models were investigated. Section 4.1 describes the evaluation criteria used in the accuracy evaluation. In Chapter 4.2, we report on the experiments and accuracy evaluation.

4.1 Experimental data The experimental data used in this paper are summarized in Table 2. The items in the Table 2 are as follows:

- Experiment Number

A number to be used in the following chapters to refer to the experimental data and contents

- Duration

The duration of the experiment

- Number of Subjects

The number of participants in the experiment

- Number of Samples

The number of samples obtained in the experiments

- Remarks

Special instructions are given.

Since the experiment may involve medical practice, safety considerations were implemented. The timing and frequency of data collection were determined by the subject at their own will. In addition, this research was conducted based on the approval of the FY 30 10 Shikoku National College of Technology Bioethics Committee and the review of research on human subjects conducted by the Graduate School of Bioengineering, Kyushu Institute of Technology (FY 2019 5th Committee).

4.2 Error Grid Analysis The accuracy evaluation in this study was performed using the Error Grid Analysis (EGA) based on the International Organization for Standardization (ISO) standard. The EGA is used to evaluate the clinical accuracy of a blood glucose meter and can examine the clinical validity of a glucose monitoring system. The true value and the predicted value of the blood glucose level are shown as a scatter chart, and the reliability of the blood glucose measuring device can be evaluated in five zones. The definition of each zone is shown in Table 3. According to Table 3, the plotted data in zones A and B are of clinically acceptable accuracy. On the other hand, the values plotted beyond region C are inaccurate and clinically

Table 3: Definition of EGA method.

Zone	Description
A	The estimated blood glucose level deviates about $\pm 20\%$ from the actual value
B	Self-monitoring device giving predictive blood glucose level degree results differ by more than 20% from actual value
C	Poor results of self-monitoring equipment
D	If detection fails, it is outside the range of actual value (70 to 180 mg/dL)
E	False blood glucose level causing serious problems in diabetes management

Figure 3: Linear regression analysis results.

Figure 4: Prediction results by neural network.

unacceptable.

4.3 Linear Regression Analysis VS Neural Network

We have compared models for predicting blood glucose levels as a result of previous studies [17]. A linear regression analysis and a neural network were used for comparison. The neural network consists of three layers: an input layer, an intermediate layer, and an output layer. At this time, two parameters calculated from Eq. 1 and Eq. 2 and blood glucose levels measured by an existing blood glucose level measuring device were used as inputs for prediction. Half of the 136 data sets were used for learning and the other half were used for testing. The samples were taken between December 2017 and June 2018 (Table 2, Experiment Number A).

An example in Fig. 3 shows the result of prediction using a linear regression analysis, and Fig. 4 shows the result of prediction using a neural network. In the case of linear regression analysis, 61.2% of the values and 33.8% of the values are plotted in zone A and zone B, respectively. In contrast, when the neural network was used, 70.5% and 29.5% of the values were plotted in zones A and B, respectively. Thus, it was confirmed that the prediction accuracy can be improved by using neural networks.

4.4 Influence of Bioinformatics on Glucose Prediction

The predictions in previous studies [17] did not take into account differences in biological information. In this chapter we investigate the relationship between blood glucose levels and gender, age, weight, and height.

Firstly, the experiments were conducted to investigate the relationship between the abovementioned parameters and the blood glucose levels. In this experiment, the measurement experiments were carried out at the health examination of Ehime Bank, Inc. in November 2018 (Table 2, Ex-

Table 4: Correlation coefficient between blood glucose level and each parameter.

Parameters	Correlation Coefficient
Age	0.412
Body weight	0.214
Height	-0.0161

periment Number B). The average blood glucose level was 96.38 mg/dL for females and 101.4 mg/dL for males, confirming that males had slightly higher average blood glucose levels. Table 4 shows the correlation coefficients between the blood glucose level and age, weight, and height. From these results, it was confirmed that there is a correlation between the age and weight and the blood glucose level, and that there is no correlation between the height and the blood glucose level. These results suggest that accuracy can be improved by predicting blood glucose levels with consideration of age and body weight.

Based on these results, the blood glucose levels were predicted in consideration of gender, age, and weight. The data used are 73 samples taken at the 32 Yumeshima Kaido Ikina Marathon held on March 3, 2019 (Table 2, Experiment Number C). Two parameters (thermal radiation and convection) and five parameters (thermal radiation, thermal convection, gender, age, and weight) were used for comparison to predict blood glucose levels. The results are shown in Fig. 5 and Fig. 6. In Fig. 5, it can be said that the prediction result is biased and the blood glucose level cannot be accurately predicted. However, in Fig. 6, 64.8% of the values are plotted in zone A, 27.0% in zone B, 2.70% in zone C, and 5.4% in zone D. Although a few values are plotted in zones C and E, most values were plotted in zones A and B, and it was confirmed that the accuracy of blood glucose level

Figure 5: Prediction results (Parameter Type 2).

Figure 6: Prediction results (Parameter Type 5).

prediction was improved by considering the added parameters. The RMSE was 35.57 mg/dL when prediction was made using five parameters.

4.5 Prediction of blood glucose levels, including heart rate

In this chapter, in addition to MHC techniques, we consider glucose prediction by introducing heart rate. From the results of previous studies [15] and up to the previous chapter, it has been confirmed that *hr* and *hc* are important values for prediction of blood glucose level. However, there are other factors that change the temperature of the fingertips besides the absorption of glucose in the body. Therefore, the current situation is considered to be the limit for accuracy to predict blood glucose levels. In addition to the MHC technique, we examined possibilities to add new parameters. A study by Kurasawa *et al.* [18] examined the prediction of fasting glucose by heart rate. Takai *et al.* [19] reported a significant difference in heart rate between healthy subjects and those with hyperglycemia. Therefore, it is considered that there is a correlation between the heart rate and the blood glucose level.

In this experiment, four parameters were obtained from the preprandial to postprandial blood glucose level, thermal radiation, thermal convection, and heart rate. We would like to monitor the variation progress of the blood glucose level until it goes down after a meal, but the number of times that the blood glucose level can be measured is limited because the existing blood glucose measuring instruments use needles. Studies by Esposito *et al.* [20] have generally reported that the peak postprandial hyperglycemia occurs 1

Table 5: Comparison with prediction including heart rate.

	<i>hr, hc,</i>	<i>hr, hc, HR</i>
RMSE of glucose level(mg/dL)	53.58	20.94

Figure 7: Forecast results (Prediction including heart rate).

hour after a meal when glycemic control is normal. Therefore, in this experiment, four measurements were performed for several days before meal, 30 minutes after meal, 60 minutes after meal, and 3 hours after meal. The sample data is 18 points from 1 subject (Table 2, Experiment Number D).

Based on these data, two types of predictions were made and compared: prediction using only heat radiation and heat convection, and prediction of blood glucose levels using heat radiation, heat convection, and heart rate. For comparison, cross-validation was performed and the model was evaluated using RMSE. The comparison results are shown in Table 5. From Table 5, it is confirmed that the accuracy of blood glucose level prediction can be greatly improved by adding heart rate. The results of accuracy evaluation using EGA are shown in Fig. 7. In Fig. 7, 77.8% of the values were plotted in zone A and 22.2% in zone B. As the number of samples is small, it cannot be asserted, but based on the results of Table 5 and Fig. 7, it is confirmed that further improvement of prediction accuracy can be expected by adding heart rate to the blood glucose level prediction using MHC method.

5. Conclusion

This paper presents an improved prediction method based on MHC method. In particular, the prediction using neural network and the possibility of adopting new input parameters were verified.

We compared linear regression analysis and neural network as glycemic prediction models. By applying the neural network, the accuracy improvement of about 10% was realized in comparison with the method using the conventional linear regression analysis. In addition, it was confirmed that the prediction accuracy drastically improved, when the glucose level prediction considering body information and biological information which were not considered in previous research was carried out. Especially, the glucose level was estimated from the relationship between heart rate and glucose level, and it was confirmed that 78%

of the values were in zone A of the EGA. We found that the heart rate is an important parameter in predicting blood glucose level to compensate for the inaccuracies of conventional MHC method. In the future, the number of data will be increased, and we expect that the accuracy of the experiment will be further improved. The presented results may solve the problem of poor prediction accuracy in non-invasive blood glucose measurements based on MHC method. In addition, in the MHC theory, it has been shown that a blood glucose level prediction method that does not require measurement of blood flow velocity can be realized.

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