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Research on the multiple linear regression in non-invasive blood glucose measurement

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Abstract. A non-invasive blood glucose measurement sensor and the data process algorithm based on the metabolic energy conservation (MEC) method are presented in this paper. The physiological parameters of human fingertip can be measured by various sensing modalities, and blood glucose value can be evaluated with the physiological parameters by the multiple linear regression analysis. Five methods such as enter, remove, forward, backward and stepwise in multiple linear regression were compared, and the backward method had the best performance. The best correlation coefficient was 0.876 with the standard error of the estimate 0.534, and the significance was 0.012 (sig. <0.05), which indicated the regression equation was valid. The Clarke error grid analysis was performed to compare the MEC method with the hexokinase method, using 200 data points. The correlation coefficient R was 0.867 and all of the points were located in Zone A and Zone B, which shows the MEC method provides a feasible and valid way for non-invasive blood glucose measurement.

Keywords: Non-invasive blood glucose measurement, metabolic energy conservation, multiple linear regression, Clarke error gird, sensor

1. Introduction

Diabetes mellitus as a chronic disease often causes metabolic disorders such as saccharides, fat, protein, electrolyte and water. Up to now, there is no method which can cure diabetes thoroughly. Diabetics are suggested that the glucose value should be tested four times per day at least. The testing methods are invasive or minimally invasive, painful, easy to infectious. If a blood glucose meter could give a testing result without blood taking, the diabetics would no long suffer from pain, fear and infection when they measure their blood glucose value for themselves.

The non-invasive blood glucose measurement methods are studied worldwide at present and they mainly contain optical and non-optical technologies. The optical technologies have been studied several years, such as Raman Spectrum, near infrared spectrum, mid-infrared spectrum, polarimetry, optoacoustic detections and so on [1-9]. Unfortunately, these technologies have common drawbacks in

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sensitivity and accuracy. The non-optical technologies include the metabolic heat conformation (MHC) method, the metabolic energy conservation (MEC) method and so on. In this paper, five methods such as enter, remove, forward, backward and stepwise in multiple linear regression for non-invasive blood glucose measurement based on MEC method are discussed and the clinical trial shows the MEC method provides a feasible and valid way for non-invasive blood glucose measurement.

2. Detection principle and sensor design

The MEC method is a non-invasive, non-optical technology for blood glucose measurement. It is a modified mathematical model from the MHC method.

2.1. Metabolic energy conservation method

The MHC method [10] was proposed by Ok Kyung Cho. It is based on the homeostatic circadian rhythm of human. The MHC method supposes that there is a subtle balance among the heat generated by glucose metabolism, local glucose value in capillary and oxygen supply. However, the blood glucose value can be estimated by heat dissipation and oxygen supply. The heat dissipation includes heat convection and heat radiation. The oxygen supply can be calculated by blood flow rate, hemoglobin concentration, and oxyhemoglobin concentration [11].

The MHC method was modified by ZC Chen, and the MEC method [12] was proposed. The MEC method supposes that the energy generated by glucose oxidation equals to the energy dissipated in local tissue of human body during a short time. The energy generation depends on the blood glucose value and oxygen supply. The energy dissipation depends on heat conduction, heat radiation, heat convection, heat evaporation, cell anabolism, muscle contraction, and excretion in local tissue. During a short time, the cell anabolism, muscle contraction, and excretion are very weak. So these parts of energy can be ignored. The oxygen supply depends on blood flow volume, pulse rate, and oxyhemoglobin saturation. Comparing the MEC method with MHC method, the essence of the two methods is the same. Both of them are based on the subtle balance of heat or energy. However, the MHC method ignores the heat evaporation and heat conduction, which may cause error when the temperature of the local tissue is higher than 25℃, since the inductive evaporation occurs in this tissue. In order to simplify the measurements of physiological parameters and the algorithm, the oxygen supply is calculated by blood flow volume, pulse rate, and oxyhemoglobin saturation in the MEC method, since the detections of hemoglobin concentration and oxyhemoglobin concentration are complicated. The pulse rate is taken into account for a more accurate estimation of oxygen supply in the MEC method [13].

According to the MEC method, the non-invasive blood glucose measuring sensor was designed and developed. It can estimate the blood glucose value after four physiological parameters, such as the heat metabolic rate, the oxyhemoglobin saturation, the blood flow volume, and the pulse rate are detected from human fingertip non-invasively. The heat metabolic rate is a representational parameter of the heat dissipation.

In human fingertip, blood glucose is oxidated to energy, carbon dioxide and water. The metabolic energy is almost disappeared by heat conduction, heat radiation, heat convection and heat evaporation in the local area of fingertip. This disappeared energy and the oxygen level in blood can be measured by the non-invasive blood glucose measurement sensor (see Section 2.2), and then the amount of blood glucose can be calculated. On the basis of the MEC method, the mathematical model for blood glucose measurement was set up as follows:

$$GLU=F_1(M,SPO_2,BF,PF,c) \tag{1}$$

Where GLU is the blood glucose value; M is the heat metabolic rate; SPO_2 is the oxyhemoglobin saturation; BF is the blood flow volume; PF is the pulse rate; c is a constant; and F_1 is the function for non-invasive blood glucose measurement.

2.2. Sensor design

The non-invasive blood glucose measurement sensor (see Figure 1) was designed based on the MEC method and the mathematical model mentioned above. In Figure 1, 1 and 6 are the humidity sensors and they detect the humidities of surroundings and near-fingertip, respectively. 2, 3, 5 and 7 are the temperature sensors and they detect the temperatures of the surroundings, the far-end of the metal sheet, the near-end of the metal sheet and the fingertip surface, respectively. 4 is the metal sheet. 8 is the photodiode. 9 is the dual-wavelength light emitting diode. 10 is the power interface. 11 is the data export interface. 12 is the thermopile infrared radiation sensor. The type of the temperature sensor is LM35CAH. The type of the humidity sensor is HIH4000-3. The type of the thermopile infrared radiation sensor is A2TPMI334-L5.5OAA060. The metal sheet is made of magnesium. When measuring, the tip of forefinger should be put into the cavity between 8 and 9, and the second and the third forefinger knuckles should be put onto the upper surface of 6 and 7.

3. Algorithm and experiment

The parameter M in Eq. (1) cannot be detected by the non-invasive blood glucose measurement sensor directly. So it should be refined to three other parameters, such as the temperature difference between the fingertip and the surroundings, the humidity difference between the near-fingertip and the surroundings, and the radiation temperature difference between the fingertip and the ambient, which can be detected conveniently.

3.1. Multiple linear regression

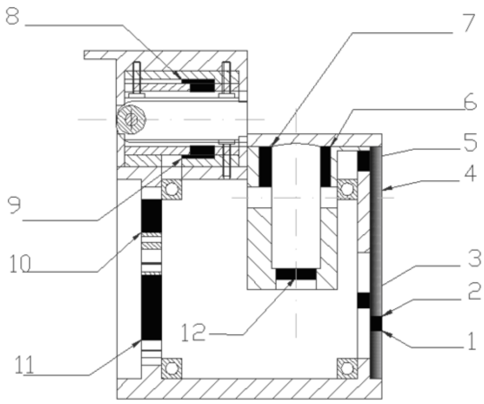

Fig. 1. The design drawing of non-invasive blood glucose measurement sensor.

According to the MEC method and the sensor design, Eq. (1) can be modified as follows:

$$GLU=F(\Delta T,\Delta RH,\Delta R,SPO_2,BF,PF,c) \quad (2)$$

Where ΔT is the temperature difference between the fingertip and the surroundings; ΔRH is the humidity difference between the near-fingertip and the surroundings; ΔR is the radiation temperature difference between the fingertip and the ambient; F is the function for non-invasive blood glucose measurement. The other parameters have the same meanings as in Eq. (1) respectively. ΔT, ΔRH and ΔR can be detected directly by the non-invasive blood glucose measurement sensor. SPO_2 and PF can be calculated by the dual-wavelength photoplethysmography [12]. BF can be achieved from the variations of the temperatures between the near-end and far-end of the metal sheet, according to the principle of thermal diffusion [11]. According to Eqs. (1) and (2), the blood glucose value has relationships with the physiological parameters, such as the heat metabolic rate, the oxyhemoglobin saturation, the blood flow volume, and the pulse rate. There is a biological background of the relationships. The glucose is the main substance of energy source for human and the blood glucose is oxidated to energy, carbon dioxide and water. So the blood glucose value depends on the energy and the amount of oxygen. If the amount of oxygen is constant, the blood glucose value will increase as the energy generation increases. Similarly, if the energy generation is constant, the blood glucose value will increase as the amount of oxygen decreases. Furthermore, the heat metabolic rate is a representation of energy generation, which includes four factors, such as heat conduction, heat radiation, heat convection and heat evaporation. By the non-invasive blood glucose measurement sensor, the parameters ΔT, ΔRH and ΔR can be detected directly. The heat conduction and heat radiation have a positive correlation with ΔT. The heat radiation has a positive correlation with ΔR. And the heat evaporation has a positive correlation with ΔRH. However, the amount of oxygen has positive correlations with the parameters SPO_2, BF, and PF. For example, if the SPO_2 and PF are constant, the amount of oxygen will increase as the BF increases.

In order to simplify to mathematic model of the blood glucose value measurement, two assumptions were made. The one was the parameters, such as ΔT, ΔRH, ΔR, SPO_2, BF, and PF had linear relationships with the parameter GLU. The other one was there were not linear dependence among the parameters, such as ΔT, ΔRH, ΔR, SPO_2, BF, and PF. On the basis of Eq. (2), the blood glucose value can be estimated by multivariate statistical analysis method such as multiple linear regression. The regression model can be established as follows:

$$GLU=a_1\Delta T+a_2\Delta RH+a_3\Delta R+a_4SPO_2+a_5BF+a_6PF+c \quad (3)$$

Where a_1 to a_6 are regression coefficients. The other parameters have the same meanings as in Eq. (2) respectively.

In order to obtain the regression coefficients, the calibration experiments were performed in the laboratory. The room temperature was 24 centigrade, and the relative humidity was 75%. 60 volunteers participated in the calibration (see Table 1). In Group One, 17 male and 13 female volunteers took part in the fasting measurements. The fasting time was at least 12 hours. In this part of volunteers, there were 25 diabetics and 5 healthy persons. In Group Two, 20 male and 10 female volunteers joined the measurements one hour after meal. In this part of volunteers, there were 23 diabetics and 7 healthy persons. 300 measurements were taken in each group. The metabolic parameters of their fingertips were detected by the MEC method, and then their blood glucose values were obtained with the hexokinase method on the Abbott Freestyle Freedom blood glucose meter.

Table 1

Demographics of volunteers in calibration experiments

Group	No. of volunteers	Gender	No. of measurements	Diabetic	Fasting
1	30	Male=17	300	Yes=25	Yes,
		Female=13		No=5	Fasting time=12 hours
2	30	Male=20	300	Yes=23	No,
		Female=10		No=7	1 hour after meal

Table 2

The results of multiple linear regression analysis

Group	Method	R	R^2	Adjusted R^2	Std. Error	Sig.
1	Enter	0.721	0.520	0.475	1.763	0.074
	Remove	0.616	0.379	0.320	2.576	0.083
	Forward	0.813	0.661	0.583	0.937	0.034
	Backward	0.857	0.734	0.699	0.642	0.017
	Stepwise	0.831	0.691	0.612	0.757	0.027
2	Enter	0.753	0.567	0.476	1.263	0.063
	Remove	0.632	0.399	0.321	2.178	0.071
	Forward	0.837	0.701	0.623	0.741	0.025
	Backward	0.876	0.767	0.691	0.534	0.012
	Stepwise	0.854	0.729	0.654	0.623	0.019

There was an assumption that the blood glucose value was changeless during the experiment for each volunteer.

The raw data were imported to SPSS 19.0, and then they were processed by the multiple linear regression after pre-process. The pre-process was parameter normalization. Each parameter was normalized to the interval 0 to 1. The shift and range transformation method can be used in the parameter normalization. There are five methods such as enter, remove, forward, backward and stepwise in multiple linear regression. The data process contained four steps. Firstly, the raw data should be imported to SPSS correctly. Secondly, the raw data should be normalized to the interval 0 to 1. Thirdly, a specific regression method should be given. Fourthly, apply the method to the data. The results are shown in Table 2. Five methods listed in Table 2 were applied to the raw data of each group. The best results were obtained by the backward method in each group. In Group One, the best correlation coefficient was 0.857 with the standard error of the estimate 0.642, and the significance was 0.017 (sig. <0.05), which indicated the regression equation was valid. In Group Two, the best correlation coefficient was 0.876 with the standard error of the estimate 0.534, and the significance was 0.012 (sig. <0.05), which indicated the regression equation was valid. The raw data were processed further with the backward method. All of the regression coefficients were acquired, and the significance of each coefficient was less than 0.05, which indicated each factor in the regression equation was valid.

3.2. Experiment and discussion

In order to check the feasibility of the MEC method, 20 volunteers participated in the experiments (see Table 3). The experiments were performed in the laboratory. The room temperature was 26 centigrade, and the relative humidity was 73%. In this group, 13 male and 7 female volunteers joined the clinical trial one hour after meal. There were 17 diabetics and 3 healthy persons. 200 measurements were taken in the trial. The metabolic parameters of their fingertips were detected by

Table 3

Demographics of volunteers in clinical trial

Group	No. of volunteers	Gender	No. of measurements	Diabetic	Fasting
1	20	Male=13 Female=7	200	Yes=17 No=3	No, 1 hour after meal

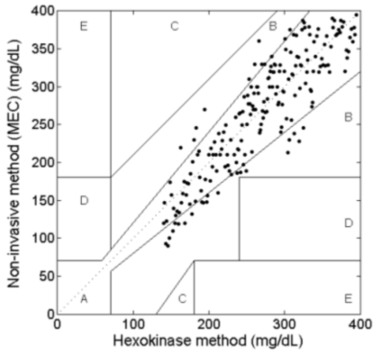

Fig. 2. Regression analysis on Clarke error grid.

Table 4

The data statistics of Clarke error grid analysis

Item	Zone A	Zone B	Zone C	Zone D	Zone E	Total
No. of points	167	33	0	0	0	200
Percentage of points	83.5	16.5	0	0	0	100

the MEC method, and then their blood glucose values were obtained with the hexokinase method on the Abbott Freestyle Freedom blood glucose meter. The non-invasive blood glucose values were estimated by the model of multiple linear regression with the backward method. The regression coefficients were derived from the model of Group Two in the calibration. The reason why the regression coefficients of the model of Group Two in the calibration were used in the experiments was that the volunteers joined the clinical trial one hour after meal, and in model of Group Two, the volunteers joined the calibration experiments one hour after meal, too. But in Group One, the volunteers were fasting.

The Clarke error grid analysis was performed to compare the MEC method with the hexokinase method, using 200 data points (see Figure 2). The blood glucose concentrations ranged from 140 $mg \cdot dL^{-1}$to 396 $mg \cdot dL^{-1}$(7.8 $mmol \cdot L^{-1}$~22 $mmol \cdot L^{-1}$). The correlation coefficient R was 0.867. The number of data points in each zone was shown in Table 4. There were 167 points in Zone A, which represented accurate blood glucose results, and 33 points in Zone B, which represented acceptable blood glucose results. All of the points were located in Zone A and Zone B, which indicated the MEC method was feasible and valid for non-invasive blood glucose measurement. The experiments of fasting blood glucose measurement are in progress.

Reproducibility was tested at ten intervals over 30 minutes for fasting healthy individuals. The coefficient of variation (CV) was 5% at the mean glucose value of 104.4 $mg \cdot dL^{-1}$ (5.8 $mmol \cdot L^{-1}$). Since relatively stable blood glucose value could be acquired only from fasting healthy individuals, reproducibility was tested in the normal blood glucose range. In successive study, the hypoglycemic and hyperglycemic values will be evaluated in the reproducibility tests.

4. Conclusion

According to the MEC method, a non-invasive blood glucose measurement sensor was designed and developed. The physiological parameters of human fingertip can be measured by various sensing modalities, and blood glucose value can be calculated by the multiple linear regression analysis. Five methods in linear regression were compared, and the backward method had the best performance. The clinical trial showed the MEC method provided a feasible and valid way for non-invasive blood glucose measurement. More clinical tests are currently ongoing to further modify the performance of the sensor, and other multivariate statistical analysis methods will be applied to the raw data process.

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