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Full paper

Non-Invasive Blood Glucose Measurement Using Temperature-based Approach

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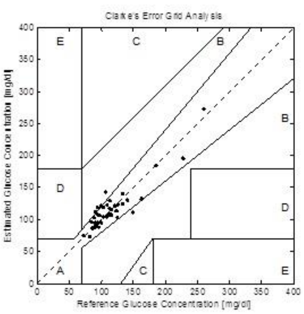
Graphical abstract



Abstract

Conventional way of measuring glucose level using finger pricking method does not only cause pain but is also costly to diabetic patients since the lancet and test strip is not reusable. Addressing to this matter, a simple metabolic heat conformation (MHC) technique was adapted in our study to measure human glucose level using non-invasive method which is harmless and capable of providing real time monitoring. This method is adapted based on the theory of glucose metabolism process which produces adenosine triphosphate (ATP). ATP function to transport energy within cells in form of heat dissipated throughout human body. Thus, temperature based algorithm was conducted using an implemented prototype circuit sensor which consist of pyroelectric detector and NTC thermistor to detect small variation of human and surrounding temperature. A total of 50 samples have been collected for analysis purposes. Results obtained from the temperature-based prototype glucose monitoring system using NTC thermistor (TPGMS-NTC) were compared with commercial automated glucose analyzer through Error Grid Analysis, and it was shown that glucose concentration is correlated to the total amount of heat dissipated from human body by 0.9125. About 90% of the samples taken are plotted within accurate range (region A) while 10% are plotted within acceptable range (region B).

Keywords: Non-invasive; glucose, diabetes, temperature, heat dissipation

Abstrak

Alat tradisional untuk menguji kandungan glukosa dalam darah bukan sahaja menyakitkan malah kepingan kertas ujian dan jarum yang hanya boleh diguna sekali sahaja juga menyebabkan kos penggunaan yang tinggi. Oleh yang demikian, kajian ini bertujuan untuk menerap kaedah menguji kandungan glukosa dengan mengkaitkan pelesapan haba daripada badan setiap individu yang terhasil daripada aktiviti pengoksidaan glukosa. Kajian ini telah membuktikan bahawa pengukuran suhu badan manusia mampu memberikan anggaran bacaan yang menghampiri bacaan glukosa yang sebenar. Sebanyak 50 sampel telah dikumpul untuk dianalisis dengan menggunakan graf *Error Grid Analysis*. 90% daripada jumlah sampel terletak dalam zon benar (Zon A) manakala 10% berada di zon yang boleh diterima (Zon B). Keputusan yang diperolehi daripada kajian menunjukkan jumlah pelesapan haba adalah berkait rapat dengan kandungan glukosa dalam darah dengan pekali korelasi sebanyak 0.9125.

Kata kunci: Pengoksidaan; glukosa, kencing manis, suhu, pelesapan haba

1.0 INTRODUCTION

Diabetes is one of the top ten chronic diseases worldwide. To date, World Health Organization (WHO) recorded about 347 million people worldwide are diagnosed with diabetes and this figure is predicted to increase to 552 million by 2030. Meanwhile in Malaysia, a study done by Institut Jantung Negara (IJN) shows a ratio of one in ten men and one in eight a woman is diagnosed with diabetes. Currently, there are a total of 2,029,883 people representing 11.66% of total population are living with diabetes. The reasons of this emerging trend of global epidemic are rapid increase in overweight, obesity and physical inactivity. Despite from practicing healthy diet and regular physical activity, continual glucose monitoring in diabetes management is also important to keep track of one's glucose level for several times a day depending on the severity of each individual case. Finger pricking method is the conventional way of monitoring glucose level, whereby, a sample of blood is drawn using a lancet and is placed on an enzymatic test strip to generate a glucose level reading using a glucometer. Since diabetes is known as a lifetime chronic disease, it is more convenient for diabetics to perform blood glucose measurement on their own rather than getting the test done by healthcare provider. Therefore, apart from the costly enzymatic strips that are not reusable, most diabetics experienced pain as they are required to monitor their glucose level for at least twice a day. Addressing to this problem, tremendous development can be seen for the past few decades to improve performance of blood glucose monitoring device which require less amount of blood sample, approximately $<1\mu L$. Even though this improvement helps to reduce the pain, another problem rises, which states that long term finger pricking would create a small wound that may lead to possible infection and severe sensitivity loss of fingertip. As a result, researchers began to change their interest to non-invasive approach, which mostly relates light absorption and scattering characteristic with glucose concentration.

In general, non-invasive glucose measurement is referred to measurement that does not involve blood extraction and skin penetration through a solid object [1,2] . Ideally, there are a few criteria which need to be fulfilled in order to conduct an appropriate non-invasive glucose measurements. According to [3], choice of measurement site must meet the following criteria:

a. Measurement sites must be temperature stable and temperature controllable
b. Measurement sites must contain measurable glucose concentration
c. Glucose concentration at the particular measurement sites has to have constant relation with the blood

Several suitable measurement sites that can be found in human body are the skin, forearm, wrist, earlobe as well as fingertip.

As aforementioned, early well established non-invasive methods focus on illuminating the chosen measurement sites using infrared light and analyzing the capture output light. Prediction on glucose concentration beneath the tissues is done by observing the captured light behavior such as reflection, scattering and absorption. Rather than using external light input to estimate glucose level, one promising non-invasive approach that worth noting, without the use of light is measurement through human's body temperature itself. Such method of measurement is known as the Metabolic Heat Conformation (MHC) technique. MHC is derived from the process of metabolic oxidation of glucose in human body [4]. Early research done by Hilson et al. [5] showed direct cheek temperature changes within two minutes after injecting glucose into volunteers' body. This study has been regarded as the foundation of latter research which relates body metabolism and glucose concentration level. For instance, study done by Zhang et al. [6-7] had proven that amount of glucose concentration possesses direct influence towards body temperature. Zhang et al. applied Near-Infrared spectroscopy method to correlate amount of glucose concentration with amount of light absorbed by glucose when optical probe with infrared light was bring into contact with body skin. The study was then further improved by taking account of body temperature into consideration. Result gained from this final study showed that prediction of glucose level closely resembled the actual level when temperature at measurement site was taken into consideration.

Generally, metabolic oxidation or cellular respiration is a process that takes place in the cells to alter biochemical energy from food intake into adenosine triphosphate (ATP). In other words, large molecules are break into smaller one through oxidation and thus releasing energy that is useful for cellular activity such as biosynthesis, locomotion or transportation of molecules across cell membranes. Since body heat generated through the process is a function of glucose and oxygen supply to the cells, there is a strong evidence of possibility to approximate glucose concentration with body heat and the oxygen supply [8-9]. Therefore, amount of heat dissipation rate, blood flow rate, hemoglobin and oxyhemoglobin concentration are the important parameters that contribute to glucose oxidation process, which in turn provide reliable estimation of glucose concentration. Practically, heat dissipated and blood flow rate can be attained through thermal measurement, while hemoglobin concentration is measured using at least two light sources with known wavelength [9]. In conjunction with the aims to eliminate the use of external input in this study, glucose prediction assumes that both hemoglobin and oxyhemoglobin will not affect much of the overall results [10]. This is due to the fact that normal hemoglobin concentration in male falls in the range between 13 – 18mg/dL, while female category falls between 12 – 17mg/dL. Moreover, range of variation is usually found to be 5 to 6% when subjects are in active condition [11]. Thus, it can be assumed that average value of hemoglobin and oxyhemoglobin concentration for both male and female subjects can be treated as constant, provided if the subject is in rest state during measurement process.

Heat dissipated through human body can be found in form of convection, and radiation [12]. Heat radiation rate is measurable using Stefan Boltzmann Law, given as follow [13];

$$\text{Heat radiation, } h_r = 4 \times \sigma \times \varepsilon \times T_o^3 \times (T_s - T_o) \text{ (W/m}^2\text{)} \quad (1)$$

where,
σ is Stefan Boltzmann constant, 5.67×10^{-8}
ε is the emissivity of measured surface
T_o is surrounding temperature in °C
T_s is measured surface's temperature in °C

On the other hand, heat convection rate is slightly more complicated than heat radiation rate and can be found as follow [14];

$$G = \{g \times \alpha \times (T_s - T_o) \times L^3\} / v^2 \quad (2)$$

$$R = G \times P \quad (3)$$

$$N = 0.021 \times R^4 \quad (4)$$

$$\text{Heat convection, } h_c = N \times k \times (T_s - T_o) / L \quad \text{(W/m}^2\text{)} \quad (5)$$

where,
G is Grashof number
g is gravity
α is thermal expansion coefficient
L is subject's height in meter
v is kinematic viscosity
R is Rayleigh number
P is Prandatl number, usually 0.7
N is Nusselt number
k is the thermal conductivity of measured surface

From equation (1) – (5) it is apparent that amount of heat production is significantly influence by surrounding temperature and body surface's temperature. The remaining factors related to heat production cause by glucose oxidation is the blood flow rate. Active oxidation process increases the rate of heat transmission when capillary blood vessels transfer heat to adjacent cells, which reflects the behavior of blood flow in human body, particularly in potential measurement sites. Total heat transfer can be observed through temperature variation at two end points of a known conductor when it is bring into contact with surface measurement. Figure 1 illustrates an example of blood flow measurement. Assume two end points of a conductor are denoted as Point A and B, where Point A is closest to the measurement site. As body surface touches the conductor, temperature at Point A will rises dramatically and eventually flattened once it steadily reaches body surface's temperature and eventually become stable. In the meantime, Point B too will experience slight increase in temperature due to the transfer of heat from body surface to conductor from start to end point. However, it is known that Point B has lower temperature compare to Point A due to dissipation of heat as it travels down to Point B. Hence, by calculating area difference between both curves within duration when measurement is taken (from 0s to 60s), blood flow rate can be approximated.

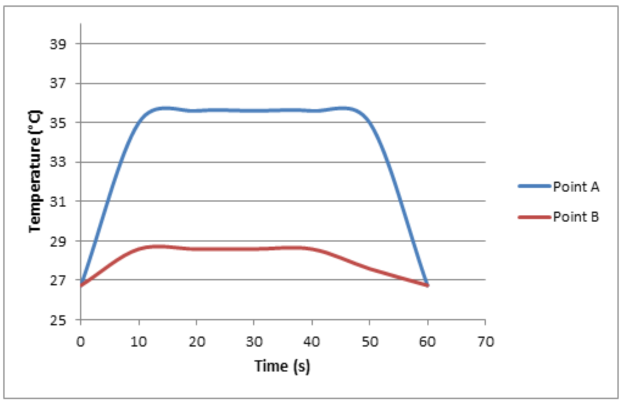


Figure 1 Heat transfer curves for Point A and B to estimates blood flow rate [10]

In this paper, the objectives are to find out how physiological parameters such as heat dissipation and blood flow rate, which has significant role in human metabolism are correlated to amount of glucose substances in the measurement. Besides, we will also attempt to apply MHC theory to propose a simple and low cost temperature based prototype glucose monitoring system using NTC thermistor (TPGMS-NTC) that is capable of giving reliable estimation of glucose concentration in a non-invasive manner.

2.0 METHODOLOGY

2.1 Data Collection

2.1.1 Implementing TPGMS-NTC

Above mentioned, highly sensitive temperature sensor are vital to detect very small variation of temperature changes in human body throughout the measurements. Therefore, glass coated NTC thermistor and pyroelectric detector are the practical choice of sensors to fulfill the need of sensitivity and reliability performance. Remote measurements of body's heat radiation can be taken using pyroelectric detector while contact temperature sensor can be done using glass coated NTC thermistor to obtain both heat convection and blood flow rate. Schematic diagram layout of whole prototype circuit is shown in Figure 2.

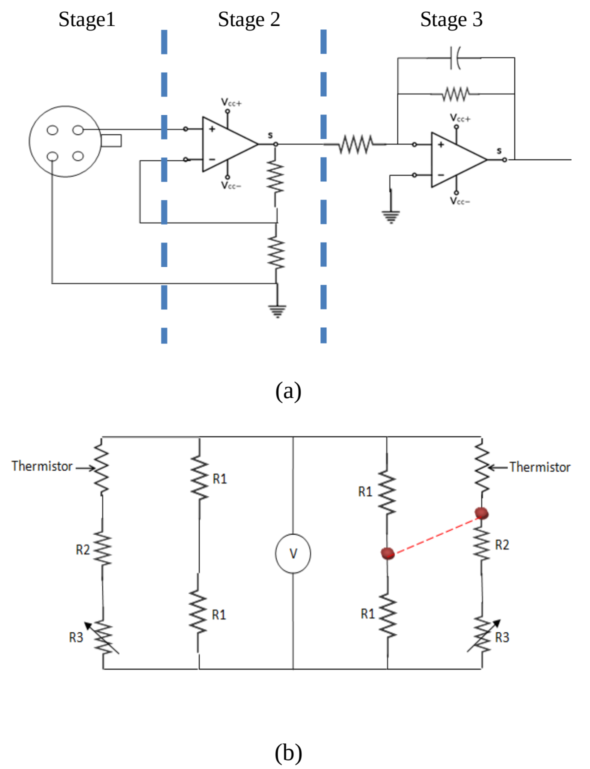


Figure 2 Schematic diagram of TPGMS-NTC. (a) Remote measurement of body's heat radiation. Stage 1 consist of a pyroelectric detector, followed by an ultra-low noise amplifier at stage 2 and lastly filter at stage 3. (b) Wheatstone Bridge circuit to measure fingertip's temperature

Since the output observed from the pyroelectric detector is in the range within mV, thus amplification is necessary so that output is detectable when performing analog to digital conversion. As seen from Figure 2 (a), output from pyroelectric detector will first undergo an amplification stage through a non-inverting ultra-low noise amplifier. Next, in order to reduce the amplified noise, a filter was cascaded as third stage to yield final reading in voltage. On the other hand, Figure 2 (b) portrays two Wheatstone bridge circuit at each side of the voltage source. Wheatstone bridge is use not only to obtain temperature values given by the thermistor, but also to ensure both thermistors is in equal temperature. When both thermistors gives same temperature reading, this means that ambient temperature is stable and that will prevent measurement results to be affected by environment changes. Originally, both branches of each Wheatstone bridge will have equal voltage since it is arrange in parallel configuration. By using simple voltage divider rule concept, when ambient temperature is stable, voltage across the dotted red line should be zero, and thus temperature reading can be acquired. Since the second Wheatstone bridge circuit is simply a replica from the first one, having zero voltage between the red dots for both bridge circuit indicates that both thermistor is now stable, as well as the ambient temperature. Thus, measurements of glucose estimation can now be taken. Consequently, Figure 3 depicts a complete TPGMS-NTC.

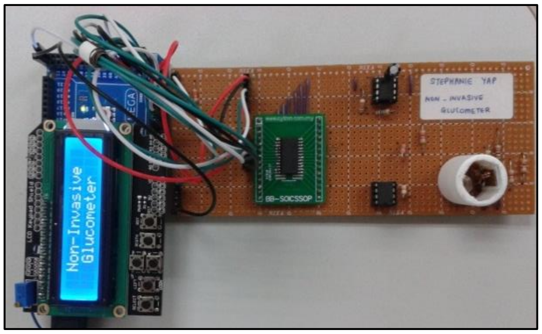


Figure 3 Top view of finished TPGMS-NTC

2.1.2 Human subject

A total of 50 samples are collected to estimate a closest possible relation between actual glucose concentration and heat dissipation rate from body's surface. Volunteers who took part in this study consist of 8 females and 5 males, age range from 24 to 56. Two from the female volunteers are recognized as diabetic patients

2.1.3 Experimental control

As mentioned earlier, surrounding temperature control is strictly regulated to ensure measurements are taken under minimum ambient influence. Surrounding temperature must be kept in range between 25 - 30°C to avoid influencing volunteer's body temperature. In cold environment, human body reacts by reducing in blood flow to preserve body heat, meanwhile, body temperature can be reduced by perspiration at ambient temperature above 30℃, resulting incorrect measurement of heat generated.

2.1.4 Data acquisition

Invasive and non-invasive measurements are conducted simultaneously on volunteers' fingertip. Invasive measurements are done using Optium Xceed glucose analyzer from Abott to provide a reference value when comparing estimated and actual glucose level. Complete measurements using the TPGMS-NTC require one minute to be carried out. Since all raw data yield by temperature sensors are in resistance value, analog to digital conversion is necessary in order to ensure estimated glucose level is presentable for user's view. Overall, step by step algorithm to convert usable raw data into digital display is shown in Figure 4. Additionally, measurements using conventional type of thermometer (TPGMS-CT) to replace NTC thermistor have also been conducted to validate reliability of sensors use in TPGMS-NTC.

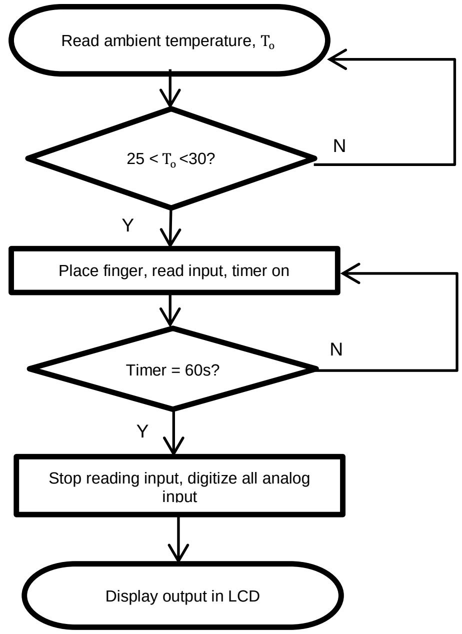


Figure 4 Analog to digital conversion algorithm to estimate glucose concentration level

2.2 Data analysis

After obtaining significant parameters such as rate of heat radiation, convection and blood flow using equation (1) to (5), relationship between these parameters and glucose level is given as;

$$\text{Glucose level} = a + (b \times h_r) + (c \times h_c) + (d \times bf) \quad (6)$$

where,
h_r is heat radiation rate
h_c is heat convection rate
bf is blood flow rate

Coefficient a, b, c and d can be found using multiple linear regression analysis.

2.3 Statistical Analysis

All data of estimation of glucose concentration using equation (6) were analyzed through Error Grid Analysis (EGA) using Matlab R2012b. EGA is convenient to be used for assessing clinical accuracy of self-monitoring glucose device. This grid consists of five distinct regions which indicate level of credibility in which the device lies in [15]. Description of each region is defined in Table 1.

Table 1 Definition of EGA's regions

Region	Description
A	Estimated glucose value deviates for about ±20% from actual value
B	Moderate outcome of self-monitoring device which gives predicted glucose value differs for more than 20% from actual value
C	Poor outcome of self-monitoring device
D	Failure to detect, whereby actual values are outside the range from 70 to 180mg/dL but estimated values are within of this range.
E	Erroneous glucose reading which may lead to significant mistakes in diabetes management

Therefore, it is desirable to attain data point plotted within region A and B which are clinically acceptable. On the other hand, region C, D and E are most likely unsafe and highly inaccurate in performing prediction of glucose level using TPGMS-NTC.

3.0 RESULTS AND DISCUSSION

Comparison between the use of NTC thermistor and conventional thermometer in TPGMS approach can be seen in Figure 5. Result shows that both methods generate acceptable range of deviation from reference value. TPGMS-NTC yield estimation of volunteers' glucose level reading of mean difference equal to 9.85mg/dL. Meanwhile, replacing NTC thermistor with conventional thermometer generates mean difference of 13.18mg/dL. Thus, it can be conclude that NTC thermistor performs with higher accuracy than conventional thermometer in estimating glucose concentration in subject's fingertip. This is because the NTC thermistor gives much faster response time and higher precision due to its capability of detecting small variation of temperature changes.

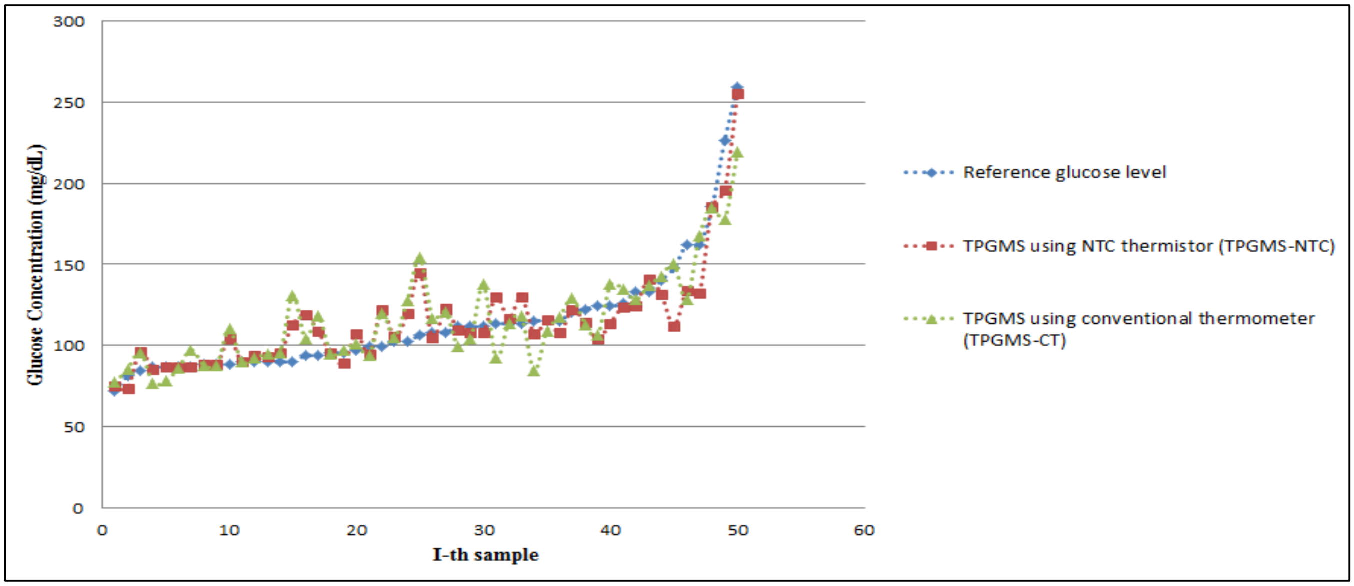


Figure 5 Comparison between glucose readings obtained using Optium Xceed, TPGMS-NTC and TPGMS-CT

Apart from that, important outcome of this study is depicts in Figure 6. Findings shows that 90% of total samples are plotted within region A, 10% in region B and neither of the samples fall into region C, D and E. This gives correlation coefficient of 0.9125. Consequently, TPGMS-NTC is believed to have the capability of generating estimated glucose concentration that is closely approximate to reference value. Even though it is said that data points within region B is considered tolerable, external factor that contribute to samples which fall into this category may cause by the hemoglobin concentration own by each subjects. As mentioned earlier, hemoglobin concentration range are clearly defined according to gender, however, each individuals possess their own personal (narrower) reference range that varies among individuals [11]. In other words, difference in exact level of hemoglobin concentration that differs among subjects and gender majorly contributes to the deviation of measured values from reference values. Overall, Table 2 summarizes the statistical parameter derived from the EGA

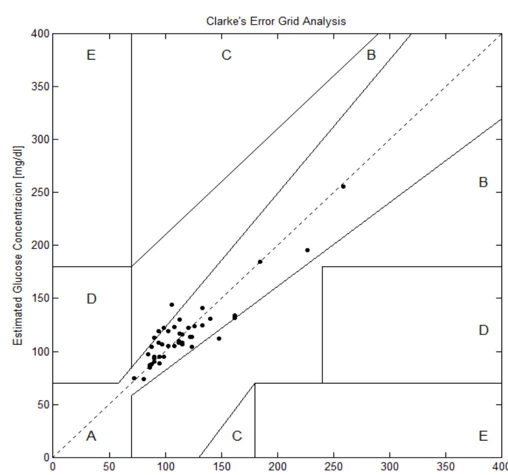


Figure 6 Result of non-invasive measurement using TPGMS-NTC in EGA

Table 2 Summary of non-invasive measurement using TPGMS-NTC in EGA

Statistic name	Value
Intercept Point (mg/dL)	18.089
Slope	0.8483
Correlation Coefficient	0.9125
R^2	0.8326
Number of samples	50

4.0 CONCLUSION

In this paper, we have presented the relationship between rate of heat dissipation and glucose concentration on fingertip skin. Positive correlation coefficient is found from statistical analysis which verifies the potential of adopting thermal measurement for blood glucose monitoring system in a non-invasive manner. Thus, it has been verified that body temperature alone is sufficient to estimate glucose concentration even without analyzing behavior of illuminated external optical light source on body skin. As a suggestion to further optimize the performance of TPGMS-NTC, it is advisable that more samples should be taken in order to achieve stronger evidence of reliability of TPGMS-NTC for continual glucose monitoring. Besides, inclusion of hemoglobin measurements will also help to minimize physical variance among individuals. Details analysis can be done individually by observing one's glucose level in a short period. This will not only result in a more in depth and specific analysis which portraits a clearer picture of the effects of metabolism related substances with glucose concentration, but also eliminating the problem of uniqueness of each individual's body system.

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