GLUCOSE CORRECTION IN HANDHELD DEVICES BY REDUCING THE EFFECT OF HEMATOCRIT

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ABSTRACT

This study presents an approach for glucose correction in handheld devices by reducing the effects of hematocrit. The hematocrit values are estimated from the transduced current curves which are produced during the chemical reactions of glucose measurement process in the handheld devices. The hematocrit estimation is performed by applying the single-hidden layer feedforward neural network which is trained by the non-iterative learning algorithm. The experimental results show that the proposed approach can improve the accuracy of glucose measurement by using the handheld devices.

Keywords: glucose measurement, handheld device, neural network, hematocrit, glucose correction.

1. INTRODUCTION

Diabetes mellitus is characterized by the inadequate ability of the pancreas to handle the blood glucose concentration. This is one of the leading diseases worldwide with the long-term complications including hypoglycemia diabetic ketoacidosis, hyperosmolar, retinopathy, cardiovascular, nephropathy (kidneys), and neuropathy (nerves and feet). The current treatment methods for insulin dependent diabetes such as continuous infusion of insulin or subcutaneous insulin injection require frequently evaluating the variation of glucose concentration.

The major tools for managing the glucose concentration are the point-of-care (POC) or handheld blood glucose meters. These meters are easy to use and relatively cheap, however they are inaccuracy in various clinical abnormalities. Many studies reported that the hematocrit is one of the most highly affecting factors for POC or handheld glucose measurements [1, 2]. A low hematocrit is associated with overestimation, while a high hematocrit is associated with underestimation of glucose results [3 - 5]. The new born may have the hematocrit levels as high as 63 % [6], and there may be 2 – 5 % of new born infants with erythrocytosis [7]. The normal glucose concentration of neonates are often lower that of adults [8], and there may be up to 20 % of neonates with hypoglycemia [9]. The hypoglycemia also occurs frequently in perioperative critically ill patients. The adult patients may have low hematocrit value, and management of

their glucose concentrations is considered as very important factor for positive clinical outcomes.

Hence, improving the accuracy of glucose measurement plays an important role to help the healthcare professionals to act intermediately certain conditions. One of the approaches for this issue is to reduce the effects of hematocrit level. Estimation of hematocrit level can be performed by employing commercial impedance analyzers with traditional centrifugation measurements. It also can be performed by dielectric spectroscopy [10]. However, the above approaches are in vitro, quite complicated or require individual devices. Recently, we developed approaches for hematocrit estimation from the transduced current curve which is generates during the chemical reaction in glucose measurement. These approaches are adequate for glucose correction in the handheld glucose meters [11, 12].

The handheld glucose meters often employ the biosensors. These biosensors use an enzyme to break the blood glucose down. It has been reported that an optical sensor could be applied to the determination of glucose content in beverage samples with good results [13] or it could be applied to the pulse hematometry [14]. However, most optical biosensors developed so far are not sensitive as the electrochemical biosensors. They also affect by the interference from some species in biological samples which result in the biosensor device very complicated in design to reduce the effects of interferences. In this paper, we investigate an approach for improving the accuracy of handheld devices in glucose measurement by reducing effects of hematocrit. The biosensors mentioned in this study is electrochemical glucose ones. The remaining parts of this paper are organized as follows. Section 2 describes the materials and methods, the experimental results and discussions are presented in the section 3, and the last section is conclusions.

2. MATERIALS AND METHODS

2.1. Effects of hematocrit (HCT) on glucose measurement

Although the handheld devices can provide quick measurements, their performance is affected by critical care variables, in which the hematocrit is the most highly effecting factor. This problem can be illustrated in Fig. 1. In Fig. 1a, three current curves from time point 11.5s to 14s provides the same value (the measured values of three curves at time point 14s are the same as 17.3439) even though glucose values corresponding to these current curves are different those are 147 mg/dL, 161 mg/dL and 157 mg/dL for the hematocrit of 27 %, 45.6 % and 39.4 %, respectively. Otherwise, with the same glucose value of 262 mg/dL, the measured values on three current curves corresponding to different hematocrit levels are different as shown in Fig. 1b.

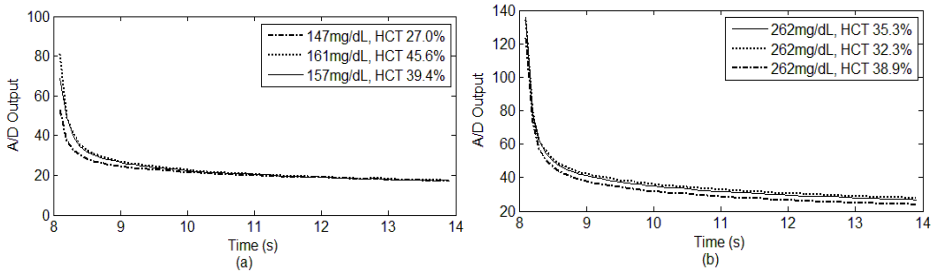

Figure 1. Effects of Hematocrit on Glucose Measurement: (a) same measured value on current curve but different glucose values, (b) different measured values on current curves but same glucose value.

Furthermore, relationship between hematocrit levels and errors of glucose measurement was also reported by researchers [14 - 16]. The results from Louie et al. [16] has shown that the difference of glucose measurements by portable device minus the primary reference glucose measurements is a function of hematocrit. Thus, in order to improve measurement performance of portable devices, the effects of hematocrit must be reduced.

2.2. Error correction for glucose measurement by reducing the effects of hematocrit

Let us denote t^{ref} be the measured glucose values from the primary glucose measurement, t^{m} be the measured glucose values from portable device, and t^{c} be the corrected glucose values of t^{m}. The main goal of correction process is to find mapping

$$\psi: t^{m} \rightarrow t^{c} \tag{1}$$

so that dependence of residuals on hematocrit is reduced as much as possible. This is illustrated in Fig. 2.

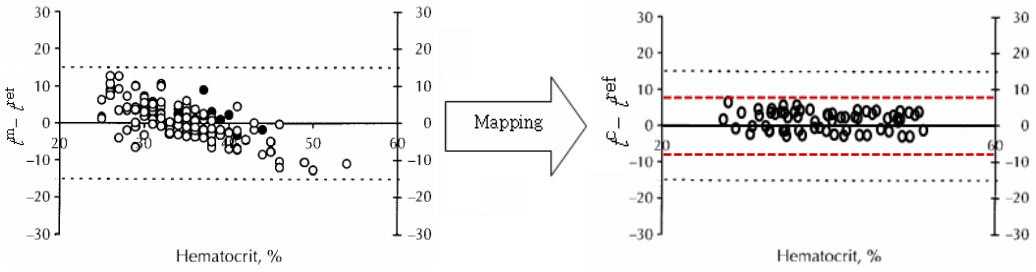

Figure 2. Glucose correction.

Denoting R^{m} be the residual which is defined as

$$R^{m} = t^{m} - t^{ref}, \tag{2}$$

the proposed mapping for ψ is given by:

$$t^{c} = t^{m} - R^{m}. \tag{3}$$

From the previous results, it showed that R^{m} is a variable which depends on the hematocrit density. Thus, there is a function g mapping from hematocrit to residuals R^{m} as follows:

$$g: HCT^{m} \rightarrow R^{m}$$

$$R^{m} = g(HCT^{m}), \tag{4}$$

where HCT^{m} is hematocrit estimated from portable devices.

In this study, the mapping function g is determined by using the linear model and the hematocrit is estimated from the transduced current curves. These curves are produced by chemical reaction between the blood and the enzyme coated on the biosensor. The enzyme commonly used in biosensors to measure the glucose levels is the glucose oxidase (GOD); it is used to catalyze the oxidation of glucose by oxygen to produce gluconic acid and hydrogen peroxide.

$$\text{Glucose} + O_2 + \text{GO/FAD} \rightarrow \text{Gluconic acid} + H_2O_2 + \text{GO/FADH}_2$$

The reduced form of the enzyme (GO/FADH2) is oxidized to its original state by an electron mediator. The resulting reduced mediator is then oxidized by the active electrode to produce a current. Figure 3 illustrates a current curve in the first 14 seconds. Normally, the first eight seconds do not contain much information for HCT estimation. In the next six seconds, the

current curves are sampled at frequency of 10Hz to produce current patterns. Let $\mathbf{x}=[x_1, x_2, \ldots, x_d]$ be a current vector of d sampled patterns from the current curve.

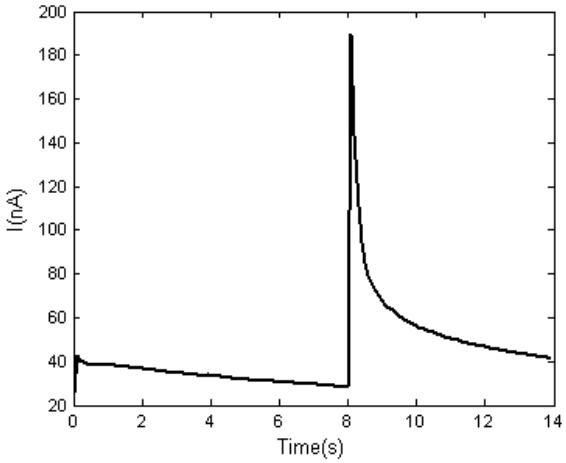

Figure 3. Anodic current curve.

In this study, the current vector is used as the input vector or neural network to determine the hematocrit. Several neural network architectures have been proposed. However, it was shown that the single hidden layer feedforward neural networks (SLFNs) can approximate any function if the activation function and the number of hidden units are chosen properly. One of the most important problems in neural networks is training. Assuming that there are n training patterns $(\boldsymbol{x}_j, \boldsymbol{t}_j)$, $j=1, 2, \ldots, n$, where $\boldsymbol{x}_j=[x_{j1}\ x_{j2}\ \ldots\ x_{jd}]^T$ and $\boldsymbol{t}_j=[t_{j1}\ \ t_{j2}\ \ldots\ t_{jC}]^T$ are the j-th input pattern and its target, respectively, the main goal of training process is to determine the network weights to minimize the error function given by

$$E = \sum_{j=1}^{n} \left\| \boldsymbol{o}_j - \boldsymbol{t}_j \right\|^2, \tag{5}$$

where $\mathbf{o}_j$ is the output vector corresponding to the j-th input pattern. An efficient algorithm for training SLFNs is extreme learning machine (ELM) which was proposed by Huang *et al.* [17]. In ELM, the minimization process of error function is based on the linear model:

$$\boldsymbol{HA} = \boldsymbol{T}, \tag{6}$$

where $\boldsymbol{H}$ is called as the hidden-layer-output matrix of SLFN and defined as [17]:

$$\boldsymbol{H}=\begin{bmatrix} f(\boldsymbol{w}_1 \cdot \boldsymbol{x}_1 + b_1) & \cdots & f(\boldsymbol{w}_N \cdot \boldsymbol{x}_1 + b_N) \\ \vdots & \ddots & \vdots \\ f(\boldsymbol{w}_1 \cdot \boldsymbol{x}_n + b_1) & \cdots & f(\boldsymbol{w}_N \cdot \boldsymbol{x}_n + b_N) \end{bmatrix}, \tag{7}$$

$$\boldsymbol{T} = [\boldsymbol{t}_1\ \boldsymbol{t}_2\ \ldots\ \boldsymbol{t}_n]^T, \tag{8}$$

and

$$\boldsymbol{A} = [\ \boldsymbol{a}_1\ \boldsymbol{a}_2\ \ldots\ \boldsymbol{a}_C]. \tag{9}$$

Note that $\boldsymbol{w}_m = [w_{m1}\ w_{m2}\ \ldots\ w_{md}]^T$ is the weight vector connecting from the input units to the m-th hidden unit, b_m is its bias, $\boldsymbol{a}_i = [a_{i1}\ a_{i2}\ \ldots\ a_{iN}]^T$ is the weight vector connecting from the hidden units to the i-th output unit, and $f(\cdot)$ is the activation function of hidden nodes. The input weights (w_m's) and biases (b_m's) of hidden units in ELM are randomly assigned, and the output weights (a_i's) are determined by

$$\hat{\boldsymbol{A}} = \boldsymbol{H}^{\dagger}\boldsymbol{T}, \tag{10}$$

where $\boldsymbol{H}^{\dagger}$ is the pseudo-inverse of $\boldsymbol{H}$. Thus, the network weights are determined by the non-iterative learning algorithm it consists of two steps: (1) randomly choose the input weights and hidden biases and (2) determine the output weights by using the pseudo-inverse operation. This algorithm can offer good performance with high learning speed in many applications.

3. RESULTS AND DISCUSSION

The data set used in our experiments was obtained from 191 blood samples from randomly selected volunteers. Each sample was applied to measure the accurate hematocrit using centrifugation method, accurate glucose using YSI2700, glucose values using handheld device (GlucoDr) and the anodic current curves. From the second part of curve, which is after the incubation period, we obtained 59 current points by sampling the current curve at the frequency of 10 Hz.

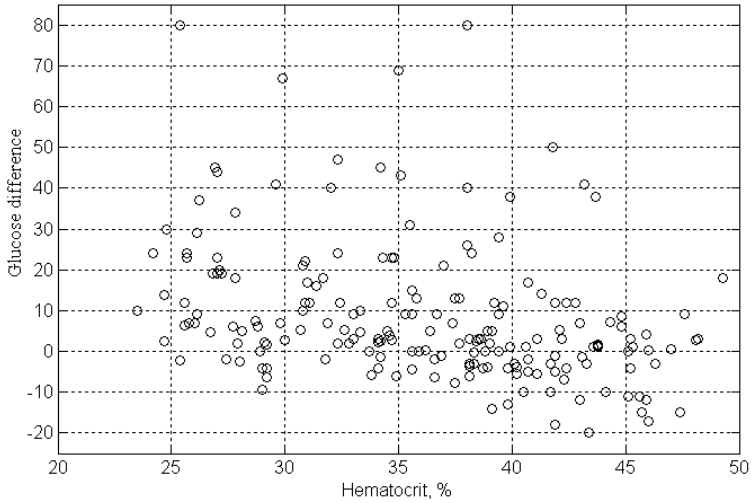

Figure 4. Plot of paired-differences of GlucoDr glucose measurements minus the YSI2007 glucose measurements.

The plot of paired-differences of GlucoDr glucose measurements minus the YSI 2007 glucose measurements against changes of collected hematocrit is shown in Fig. 4. From this figure, we can see that there is a relationship between hematocrit and residuals which are defined as differences of GlucoDr glucose measurements minus the YSI2007 glucose measurements. In addition, using the test statistic for the slope given by

$$t_{slope} = \frac{slope - 0}{\sigma_{slope}} \tag{11}$$

and using the *P*-test we see that the slope value is significantly different than 0 ($p < 0.01$). Therefore, we can conclude that effect of hematocrit on glucoDr measurements is significant which is consistent with the previous reports.

Thirty percent of data set is used for training in order to find the network parameters and the mapping function *g* from hematocrit to residuals, and the remaining 70 % is used for evaluation. The RMSE for GlucoDr on the test set without error correction is 16.4149 while that with error correction is 13.7418. The *t*-test for slope without error correction is -3.846 (p-value <

0.001) which shows dependence of residuals on hematocrit levels, while the *t*-test for slope with the error correction is 0.26, these results show that the effects of hematocrit are reduced after error correction. On the error tolerance of 15 %, without error correction give 91.6 %, while with error correction can give 94.6 %.

4. CONCLUSIONS

The handheld devices or POC are popular to measure glucose values. However, their accuracy is affected by some factors, in which the hematocrit is the most highly affecting one. This paper presents an approach for reducing the effects of HCT, in which HCT is estimated from the transduced current curve by employing the single hidden layer feedforward neural network. This network is trained by non-iterative learning algorithm. Experimental results on the handheld devices (GlucoDr) have shown the performance of correction.

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