Joint optical-electrical technique for noninvasive glucose monitoring

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In Diabetes mellitus, self monitoring of blood glucose is crucial for effective treatment since it can help identify and prevent unwanted periods of hypo- and hyperglycemia; this monitoring procedure usually involves finger-stick testing which is painful to the patient and carries the risk of infection. Non-invasive techniques, including impedance and near infrared spectroscopy, have been developed to predict glucose concentration; however, these techniques have not reached the accuracy needed for glucose monitoring. In this work a new concept which involves the combination of two spectroscopic measurements, electrical impedance spectroscopy and near infrared spectroscopy, is developed to decrease the prediction error of single-measurement non-invasive glucose monitoring systems. Electrical impedance and near infrared spectroscopy measurements were performed under controlled temperature and humidity conditions on ten non-diabetic volunteers (age 26.1 $\pm$ 3.7 years, BMI 25.24 $\pm$ 3.67 kg/m^2). The results show that all of the values predicted by the joint optical-electrical technique were clinically acceptable and the root mean squared error of prediction, which in this study was compared to a commercial glucose meter, is lower than previously published values for near infrared spectroscopy and impedance spectroscopy done separately.

Keywords: Non-invasive glucose monitoring; optical spectroscopy; electrical spectroscopy.

En la Diabetes mellitus el monitoreo de glucosa sanguínea es crucial para el tratamiento efectivo de esta enfermedad principalmente para identificar y prevenir periodos de hipo- e hiperglucemia. Este procedimiento de monitoreo generalmente involucra la obtrención de sangre por medio de una lanceta, un método que es doloroso y acarrea la posibilidad de generar infecciones. Las técnicas no-invasivas, como la espectroscopía en el cercano infrarrojo y la espectroscopía de impedancia eléctrica han sido exploradas para predecir la concentración de glucosa, desafortunadamente estas técnicas no han alcanzado la precisión necesaria para el monitoreo efectivo de glucosa sanguínea. En este trabajo se presenta un nuevo concepto que consiste en la combinación de dos tipos de mediciones espectroscópicas, espesctroscopía de impedancia eléctrica y espectroscopía en el cercano infrarrojo, con el objeto de reducir el error en la predicción no invasiva de glucosa. Las mediciones fueron tomadas en condiciones controladas de temperatura y humedad a diez voluntarios no-diabéticos (edad 26.1 $\pm$ 3.7 años, BMI 25.24 $\pm$ 3.67 kg/m^2). Los resultados indican que los valores predictivos de la técnica conjunta óptica-eléctrica son clínicamente aceptables y el error de predicción, obtenido utilizando un glucómetro comercial, es menor que los publicados anteriormente utilizando únicamente una sola técnica espectroscópica.

Descriptores: Monitoreo no-invasivo de glucosa; espectroscopía óptica; espectroscopía de impedancia eléctrica.

PACS: 42.62.Be; 87.64.km; 87.85.Ox

1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Abnormally high levels of glucose can damage the small and large blood vessels, leading to: diabetic blindness, kidney disease, amputations of limbs, stroke, and heart disease [2]; also, excessive use of glucose-lowering medication such as insulin can cause hypoglycemia or abnormally low blood sugar. According to the Mexican National Health Information System there are more than 10 million people who are currently diagnosed with diabetes, of which 90% are type II diabetics, and it is the main cause of mortality in Mexico accounting for 13.6 percent of deaths in general [3].

Frequent monitoring of glucose concentration in diabetic patients is crucial for effective treatment because it can supply trend information that could help identify and prevent unwanted periods of hypo- and hyperglycemia [4]. Self monitoring of blood glucose is usually done in an invasive manner, which involves finger-stick testing which is painful to the patient and carries the risk of infection [5]. Recently, minimally invasive needle-based continuous glucose monitoring systems that can provide glucose measurements every 5 minutes or less have become available [4].

Several techniques such as diffuse reflectance spectroscopy, electrical impedance spectroscopy, Raman spectroscopy, among others, have been used for noninvasive glucose monitoring [6]; even though these studies were performed under different environments and clinical settings they can give a rough estimate of the sensitivity and reliability of current non-invasive glucose technology. These techniques present a Root Mean Square Error of Prediction (RMSEP) that goes from 25 to 46 mg/dl [5,7,8,9,10,11,12,13,14]; which for a 126 mg/dl of Fasting Plasma Glucose level (FPG), which is considered a diagnostic criteria for diabetes [1], gives a relative concentration error higher than 15%. These studies rely on a single detection mechanism,

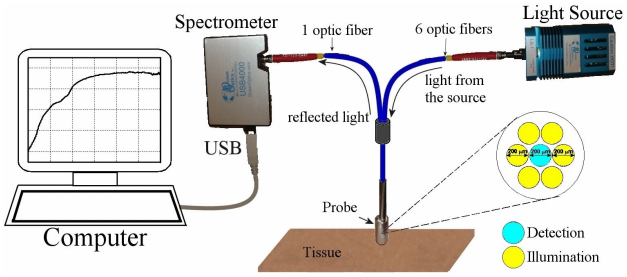

FIGURE 1. Experimental setup for the diffuse reflectance measurements.

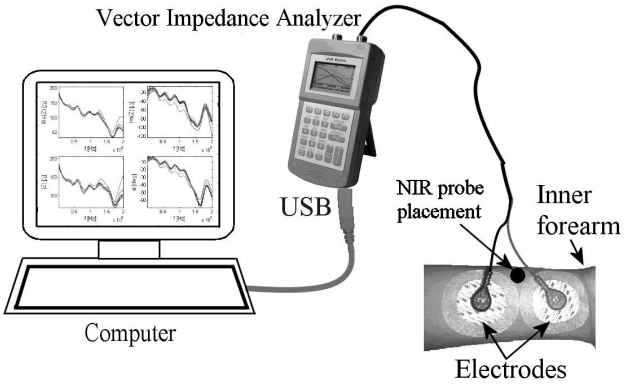

FIGURE 2. Experimental setup for the electrical impedance measurements, and NIR probe placement.

but a combination of two or more detection mechanisms to reduce the error of prediction has not been investigated.

Near infrared (NIR) spectroscopy has been used to monitor changes of glucose concentration in tissue owing to the fact that a change of refractive index takes place in the extracellular fluid due to the presence of additional glucose, which causes a small change in the overall scattering properties of the tissue that can be detected by NIR spectroscopy [15].

It has previously been reported that glucose variations affect the electrical properties of cellular membranes [14]. This is due to specific reactions of blood and tissue cells to varying glucose concentrations, which changes the electrolyte balance across the membranes of blood and underlying tissue. These changes in the electrical properties of cellular membranes result in changes in the ac conductivity and tissue permittivity which can be measured using impedance spectroscopy [16].

In this work, a new concept which involves the combination of two spectroscopic measurements, electrical impedance spectroscopy and near infrared spectroscopy, is developed to decrease the prediction error of single-measurement non-invasive glucose monitoring systems.

2. Method

Ten oral glucose tolerance tests (OGTTs), consisting of ingesting 100 g of dextrose anhydrous dissolved in 300 ml of water and measuring capillary glucose concentration every fifteen minutes, along with NIR spectroscopy and impedance spectroscopy measurements, were performed on 10 non-diabetic participants (age 26.1$\pm$3.7 years, BMI 25.24$\pm$3.67 kg/m^2) in order to correlate the spectral measurements with capillary blood glucose levels. Since both hyper and hypoglycaemic excursions lead to changes in the electrolyte balance in blood, cells, and interstitial fluid, in healthy subjects as well as in patients with diabetes [14], a decrease in the error of prediction obtained with measurements performed on healthy subjects could be extrapolated to patients with diabetes. Informed consent was obtained from all participants and the study was approved by the local ethics committee. Capillary blood glucose measurements were performed with an Accu-Check Sensor ^{TM} (Roche Diagnostics Operations, Indianapolis, IN) blood glucose monitor with a measurement range of 10-600 mg/dl and a standard error of 12.2 mg/dl in the 13.1 to 572.1 mg/dl range [15].

Diffuse reflectance spectroscopy was performed using a USB4000-VIS-NIR spectrometer (Ocean Optics, Dunedin, FL) with an optical resolution of approximately 1.5 nm full-width half-maximum (FWHM), an LS-1 tungsten-halogen light source (Ocean Optics, Dunedin, FL), and an R200-7-VIS-NIR reflection probe (Ocean Optics, Dunedin, FL). This probe consists of a tight bundle of seven optical fibers (200 μm in diameter) in a stainless steel ferrule: six of these fibers provide the illumination while the other fiber collects the reflected light. Figure 1 shows the experimental setup and provides detail on the geometry of the probe. The instrument collected intensity spectra in diffuse reflectance from the inner forearm in the wavelength range of 700 – 1000 nm. This wavelength range was chosen in order to take advantage of the "therapeutic window" where tissue absorption is low and light penetration is high [17]. The collected data was transmitted to a computer via a USB 2.0 interface for further processing.

The raw reflectance spectra was corrected for detector dark current and normalized to the spectrum obtained from the light source reflected on a white reference standard [19].

Figure 2 shows the experimental setup used for the impedance spectroscopy measurements, they were performed with a VIA Echo 2500 (AEA Technology, Carlsbad, CA) handheld vector impedance analyzer. The measurements were performed over a 1-200 MHz range using a pair of Red Dot ^{TM} disposable silver chloride electrodes (3M Health Care, St. Paul, MN) placed 4 cm apart of each other and attached to each volunteer's inner forearm. The frequency range chosen has been used successfully in previous work [16], it is high enough ($>$100 kHz) to minimize the effect of skin moisture and avoid problems with electrode polarization, and low enough ($<$200 MHz) to still allow the electric polarization of cell membranes [16]. The cable-nulling feature of the impedance analyzer was used to remove the influence of the cables in the impedance measurements in order to get more accurate readings.

NIR and impedance spectra, as well as capillary blood glucose measurements were taken in fasting conditions, at

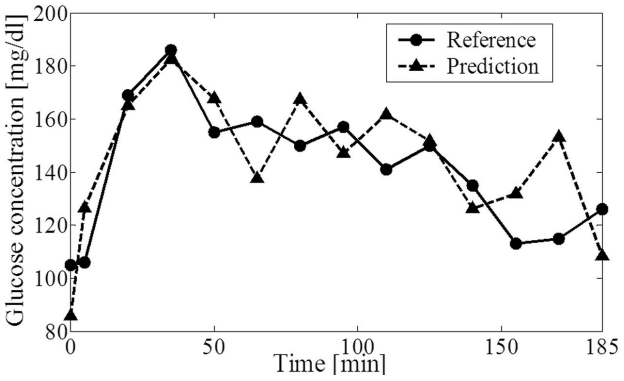

FIGURE 3. Reference and prediction time profiles for a given subject under an oral glucose tolerance test.

the initial glucose intake and every fifteen minutes over a 3 hour test for every subject. During the duration of the test, the subject remained seated with the impedance electrodes attached to its arm, temperature and humidity were also maintained constant during the 3 hour test. The impedance electrodes were placed on the inner side of the left forearm, and the optical probe was used only when the measurements were being performed, the impedance and optical measurements were taken simultaneously. The optical probe used for the diffuse reflectance measurements was located between the impedance electrodes, equidistant from each electrode center (Fig. 2).

The second derivative of the impedance spectra was obtained to enhance the relevant peaks [20], a standard normal variate (SNV) and Gaussian filtering were performed on the NIR spectra to remove offsets and multiplicative effects [21], and reduce noise, respectively.

Both NIR and impedance spectra were used as predictors in a PLS regression algorithm using The Unscrambler ^{TM} (CAMO Software AS., Oslo, Norway) commercial software.

The fourteen NIR and impedance spectral measurements taken during the OGTT along with the measured glucose reference values taken invasively were used to compute the calibration coefficients using PLS regression. An individual calibration model for each subject was developed by introducing 251 impedance points and 1675 reflectance points in a matrix of 1926 elements, each one representing the impedance or reflectance at a certain frequency or wavelength. A leave-one-out-cross-validation (LOOCV) method [22] was used to test the calibration model obtained through PLS regression for each subject. Figure 3 shows reference glucose values obtained invasively during an OGTT and the predicted values obtained from the NIR and impedance measurements using the calibration model for that specific subject. Model performance is reported as the Root Mean Square Error of Prediction (RMSEP) [23].

In this work, an individual calibration scheme was used since a universal calibration routine, which would be the preferred choice, would be very difficult to implement due to the fact that the optical and electrical characteristics of skin varies greatly from individual to individual.

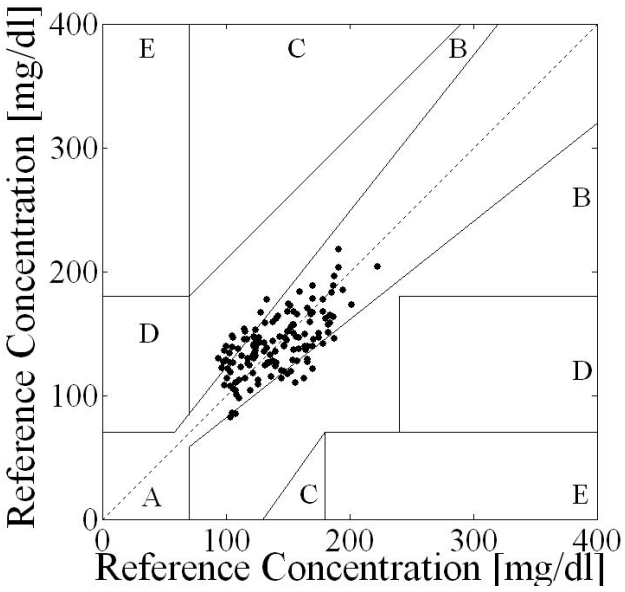

FIGURE 4. Clarke error grid analysis on the predicted glucose values obtained using a joint optical-electrical technique.

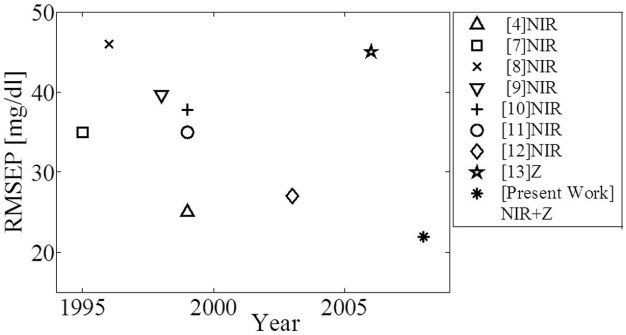

FIGURE 5. Comparison of the RMSEP value obtained using a joint optical-electrical technique (NIR+Z) with previously published values obtained using NIR spectroscopy or impedance (Z) spectroscopy separately.

3. Results

It is worth noting that the performance of the USB4000-VIS-NIR spectrometer used decreases for wavelengths above 750 nm; however, our measurements and results were reproducible in the whole 700 – 1000 nm region.

Leave-one-out cross-validation (LOOCV) is known for making efficient use of the available samples, a feature which makes them especially suitable for use in situations where only a limited number of measurements are available; therefore, this method was used to construct a model for each subject. The calibration model was verified using each excluded sample, 140 glucose prediction points were generated for the 10 subjects using their 14 NIR and impedance measurements.

The RMSEP, which is the square root of the average of prediction errors squared, is given by:

$$RMSEP = \sqrt{\frac{\sum_{n=1}^{N} (y_n - \hat{y}_n)^2}{N}}, \quad (1)$$

where yn is the reference value, $\hat{y}n$ is the predicted value, and N is the total number of samples [23].

Figure 4 shows the predicted glucose values on a Clarke error grid [24]. The calculated root mean square error of prediction (RMSEP) was 21.96 mg/dl and Clarke error grid analysis showed 77.86% of the values in zone A, 22.14% in zone B, and none in the C-E region.

4. Discussion

Even though care was taken to always put the electrodes at a fixed distance, the impedance spectroscopy measurements can be improved by using fixed-distance electrodes.

From the Clarke error grid analysis (Fig. 4) we can see that all of the predictions fell on the clinically acceptable region (A and B) and none of the predictions fell on the potentially dangerous zone (C-E).

Also, the obtained RMSEP value is lower than previously published values for NIR spectroscopy and impedance spectroscopy done separately (Fig. 5). It is worth noting that since all the studies were performed on different settings using different protocols a direct comparison between different studies is difficult to make; however, these results can give a rough comparison of how our method compares to other non-invasive techniques.

It is also worth noting that the low RMSEP value reported in the present study was obtained by comparing the predicted glucose values with measurements made with a commercial glucose meter which, even though should provide results within 20% of laboratory standards, it is not considered the gold standard for glucose measurements. However, the novelty of the present study is based on the fact that a joint optical-electrical technique can prove useful in future non-invasive glucose meters.

Taking into account the previous statement, the results obtained in this work provide evidence that a joint optical-electrical technique can predict noninvasively capillary glucose concentrations more accurately than optical or electrical techniques performed separately. One of the shortcomings of this technique is that an individual calibration routine is needed, while the use of a universal calibration routine would be more appropriate for non-invasive glucose monitoring; however, due to the fact that optical and electrical characteristics of human tissue vary significantly between individuals a universal calibration routine would be difficult to implement.

Leave-one-out-cross-validation method can be influenced by several external factors, including chance correlation, which has been regarded as one of the most severe obstacles in the noninvasive measurement of blood glucose [25]. Therefore, further studies should be carried out to evaluate the joint optical-electrical technique in long term tests and in diabetic subjects.

Acknowledgments

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