Pulse Glucometer

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***Abstract* – This paper describes the development and the clinical evaluation of a continuous non-invasive monitoring device for blood glucose concentration in arterial blood. The adopted method was the same one used in pulse oximetry for determining arterial blood saturation. The measurement system developed in this project to determine pulse blood glucose level was based on an optical sensor similar to the pulse oximetry sensors using wavelengths of 805 and 1350 nm. A clinical trial of the device was performed with 20 volunteers, both male and female, aged 16 to 63, weighting 48 to 112 kg and of different races. For this group of volunteers the device presented an accuracy (Arms) e standard deviation (SDR) in the magnitude of 10 mg/dl, considered very good when compared to blood glucose monitors of the "fingertip" type, which presents a reading accuracy in the magnitude of 15 mg/dl for the range of measurements employed.**

***Index Terms*— Blood Glucose monitoring, Non-invasive measurement, Diabetes, Near-infrared**

I. Introduction

CAPILLARY blood glucose level (the concentration of glucose in the blood) measurements are gaining more and more importance as a tool for patients controlling diabetes, but there are still limitations, such as patient adhesion to treatment and incomplete data from very few measurements taken throughout the day. As a result, new measurement methods and processes and more comfortable devices for the continuous measuring of blood glucose levels are being researched, since a single blood glucose level test such as the ones currently performed in clinics does not provide enough information for good patient evaluation. A lot more is necessary to keep diabetes well controlled, and several measurements of glucose levels are necessary to adjust treatment according to each patient's needs.

The developed device is based on a completely non-invasive, painless and discomfort-free method for continuous monitoring of glucose concentration in arterial blood using the same method as pulse oximetry [33, 34].

Pulse oximeters became commercially available in the 80s and have experienced an enormous growth in use ever since because the information they supply allows the early discovery of problems in oxygen supply to tissues. Oximeters estimate the saturation of oxygen in arterial blood, providing vital information about the patient's cardio-respiratory system. Pulse oximeters estimate the saturation of oxygen in a simple, non-invasive form, directly in arterial blood, hence the motivation for this study.

A lot of research is being made about blood glucose level measurements, and devices which analyze glucose concentrations in interstitial liquid using micro surface plasmon resonance sensor [1] and micromachine amperometric cells [2] have been proposed. A glucose sensor using biocompatible polymers was also proposed [3], and devices employing micro-electro-mechanical systems (MEMS) have been suggested by Zhao et al. [4] and Huang et al. [5]. Sensors using the eyes as measurement sites have also been divulged [6, 7]. Liu et al. [8] proposed a subcutaneous sensor using reverse iontophoresis. Jacobs et al. [9] studied otoacoustic emission with blood glucose levels, Lumbroso et al. [10] developed a bioimpedance sensor for glucose recognition, whereas Maruo et al. [11] have published an article describing a system using near-infrared, Chaudhary et al. [12] used dissolved core alginate microspheres as "smart-tatto" for glucose measurements, Park et al. [13] used a non-enzymatic glucose sensor, Lee and Cui [14] built layer-by-layer self-assembled single-walled carbon nanotubes and Garret et al. [15] developed PH-insensitive glucose indicator, among many others. The measuring methods adopted in those studies differ in their proposed instrumentation methods because they do not use optics as a measurement principle, or because they do not use the pulsing characteristic of arterial blood in the described methods.

Several studies were also found regarding the development of a non-invasive instrument for blood glucose concentration measurements, especially those using infrared spectroscopy [16]. Recently, Yamakoshi et al. [17-20] developed a new technique for non-invasive measurements using the pulsing characteristic of blood, covering the wavelength from 900 to 1700nm, scanning at a maximal spectral rate of 1800 spectra/s, with a minimum exposure time of 20 μs, differing from the method proposed in this article, which employs only two fixed wavelengths to perform the measurements.

Several other studies also used spectroscopy as basis for measuring blood glucose concentration [21-27]. Maruo et al. have also been researching the use of near-infrared [28-32], but those (and some others) do not use the pulsing characteristic of arterial blood.

No patents were found to use the same measuring method for pulse glicosimeters as the one in this study.

Patents of non-invasive methods to estimate blood glucose concentration have been found, however, based on the speed of sound through blood and conductivity and technical capacity of blood for such. Patents for manufacturing methods

of test strips for glucose measurements in blood samples with measurement devices of the "fingertip" type were also found.

Several of the other patents found describe, as yet, invasive methods for measuring blood glucose levels, which also employ test strips that need dark or limited lighting environments.

The search also yielded patents which propose non-invasive methods using several light sources, but which do not use the pulsing characteristic of arterial blood, only the DC levels of transmission for each light source. There are also methods proposed for the continuous monitoring of blood glucose which use light emission through blood, but those use implanted sensors.

Several other patents prescribe methods which do not employ light emission through arterial blood, such as colorimetric methods, conductive adhesives, fluorescent contrasts, (implanted) electric-chemical sensors, implants, specific reagents, other physical parameters and biosensors.

In conclusion, a broad search of world patents and articles was made, and no other publication or patent suggesting a similar method to the one presented in this paper was found. Therefore, an international patent has been requested by the authors.

II. Materials and Methods

The Beer Law (also called Beer-Lambert Law or Bouguer Law) describes the attenuation of light passing through a uniform medium which contains an absorbent substance. If monochromatic light with an intensity I_0 falls upon a medium, part of this light is transmitted through the medium and another part is absorbed. The intensity I of light propagating through the medium is reduced exponentially with distance, according to the following equation:

$$I = I_0 e^{-\varepsilon(\lambda)cd} \tag{1}$$

where ε(λ) is the extinction or absorption coefficient of the absorbent substance for a specific wavelength λ, c is the concentration of the absorbent substance, which is constant for the medium, and d is the length of the optical path through the medium.

Transmittance (T) of light propagating through a medium with an absorbent substance is defined as the ratio of transmitted light I to incident light I_0, i.e.,

$$T = \frac{I}{I_0} \tag{2}$$

The absorbance which is not dispersed in this process, normally referred to simply as absorbance (A), is defined by:

$$A = -\ln(T) = \varepsilon(\lambda)cd \tag{3}$$

The Beer Law properties are also valid if more than one light absorbent substance is present in the medium. Each absorbent contributes its part to the total absorbance. The mathematical representation of this absorbent system is defined by the superposition of the individual absorbents, i.e., the total absorbance A_t resulting from the travel of light in a medium with n absorbent substances is the sum of the n independent absorbances, according to the following equation:

$$A_t(\lambda) = \varepsilon_1(\lambda)c_1d_1 + \varepsilon_2(\lambda)c_2d_2 + \ldots + \\ + \varepsilon_n(\lambda)c_nd_n = \sum_{i=1}^{n}\varepsilon_i(\lambda)c_id_i = \sum_{i=1}^{n}\varepsilon_i(\lambda)c_id \tag{4}$$

where d is the length of the optical path, which is constant for all substances and wavelengths.

Therefore, the Beer Law enables the determination of unknown concentrations of n different absorbent substances in a homogeneous medium, if light absorbance is measured for n different wavelengths and if the extinction coefficients of the substances are known. Thus, the concentrations are provided by the solution of a system with n equations and n variables.

The proposed instrument determines the concentration of arterial blood glucose using the measurements of light absorbance in live tissues with two different wavelengths (λ_1 e λ_2). Considering that all other absorbents will maintain their concentrations constant, a system of 2 equations and 2 variables is obtained.

The method also uses the effect of the arterial pulse to differentiate the arterial blood absorbance from the one presented by the other absorbents. The arterial pulse is related to the cardiac cycle.

Light propagating through biological tissues (such as the finger or the earlobe) is absorbed by different absorbent substances. The light absorbents in the region of interest are skin pigmentation, bone, arterial blood and venous blood.

Arteries contain more blood during systole than during diastole and, therefore, their diameter increases during systole due to the increase in pressure. Such effect takes place in arteries and arterioles, but not in veins. Light absorbance in tissues containing arteries increases during systole, mainly due to the increase in the amount of absorbent substances and also because the length of the optical path increases. This alternating portion of the total absorbance, corresponding to the relative absorbance due to the pulsing component or arterial blood and referred to as the alternated component of the total absorbance AC, is distinct from the absorbance in venous blood, of which there is a constant amount in arterial blood, and from the absorbance in other non-pulse components, such as skin pigmentation, which constitute the continuous component of the total absorbance DC, i.e.,

$$A_t = f(AC, DC) \tag{5}$$

The alternated portion of the light absorbed by live tissues normally does not exceed 1% to 2% of the constant absorbance [33]. The electrical signal resulting from the transmitted light, which varies over time, is known as the pletismographic signal.

The intensity of light propagating through a tissue during diastole is high (I_H). The absorbents present during diastole are related to the continuous DC component of total absorbance. The diameter of arterial vessels is minimum, the absorbance relative to arterial hemoglobin is minimum and the amount of light transmitted is large (I_H), presenting a peak such as the one in Fig. 1.

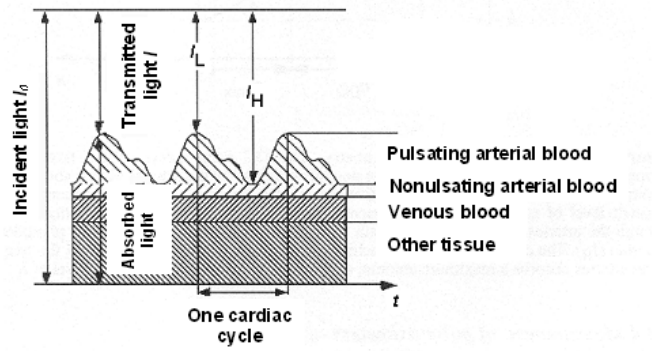

Fig. 1. Light absorption and transmission in live tissues [33].

Different reasons account for the choice of wavelengths used to determine glucose concentration on arterial blood. The red pigmentation of skin absorbs most of the light with wavelengths bellow 600nm and, therefore, it is not appropriate to measure light absorbance in this range. The wavelength of 805nm was used as a reference, since there is low influence of hemoglobin at this value because the spectral absorbance curves for reduced hemoglobin and oxygenated hemoglobin present relatively flat and close segments [35], as presented in Fig. 2, where the crossing of the oxyhemoglobin and reduced hemoglobin curves is clearly shown.

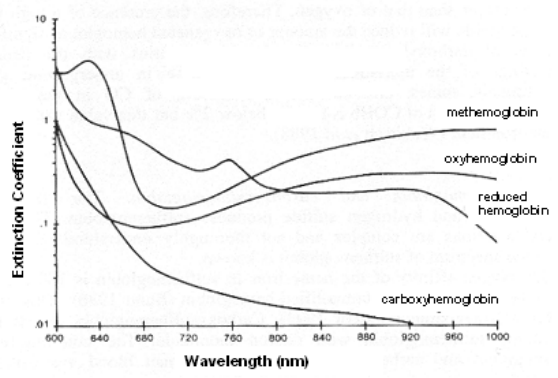

Fig. 2. Extinction coefficients for the most common types of hemoglobin [33].

Fig. 3 shows the absorbance of the glucose molecule for the wavelengths of interest in the instrument proposed to measure glucose concentration in arterial blood.

Wavelengths of 1400nm to 2400nm [36] are necessary to obtain significant variations in light transmitted through glucose. Thus the wavelength of 1350nm was chosen due the current availability of commercial diodes for light emission of this value, close enough to the recommended range.

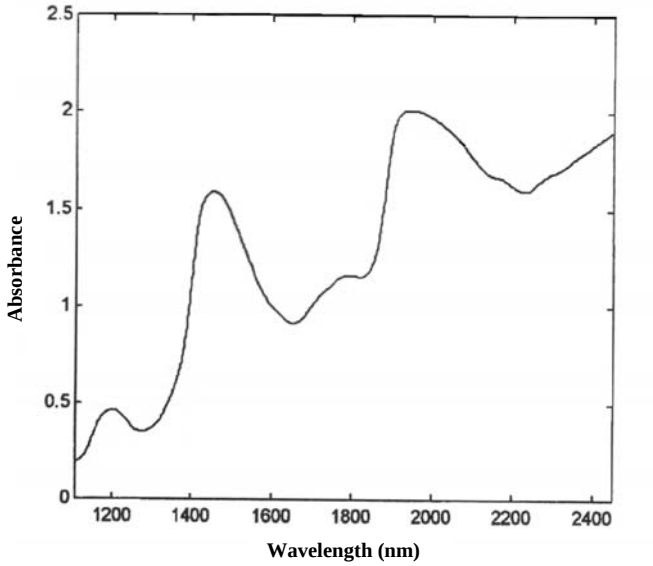

Fig. 3. Extinction coefficients for glucose [36].

The readings in the pulse glucometer will be an estimate of the glucose concentration in arterial blood derived from the Beer Law as a function of the ratio of absorbances in two wavelengths, i.e.,

$$C_G = f\left(\frac{At_1}{At_2}\right) \tag{6}$$

Due to the non-linearity of LEDs, photodetectors and light absorbance in tissues, the absorbances At_1 e At_2 must be normalized with a ratio [33]. The intensity of light measured for a given wavelength λ must be normalized before it is compared to the results of the measurement performed for another wavelength, due to the fact that each LED emits light with different intensities as a function of λ, due to the absorbance characteristics of the continuous components and to the sensitivity of photodetectors and due to variations in tissue absorption and absorbent length from one patient to the other [37]. The normalized signal I_n is calculated by dividing the intensity of transmitted light by the value of its maximum peak in the cardiac cycle ($I_{H,1}$ for the wavelength of 805nm and $I_{H,2}$ for the wavelength of 1350nm), according to equation 7:

$$I_n = \frac{I}{I_H} \tag{7}$$

The transmitted light intensity signals normalized for both wavelengths are independent from the level of incident light and from the non-linearity of the photodetector, as shown in Fig. 4. An AC component of the normalized signal only represents the variation in transmitted light caused by the pulsing of arterial blood and can be compared to other AC components. Those AC components depend on the absorbents present in arterial blood (Glucose and Others) e on the optical length *d* by the variation in artery volume.

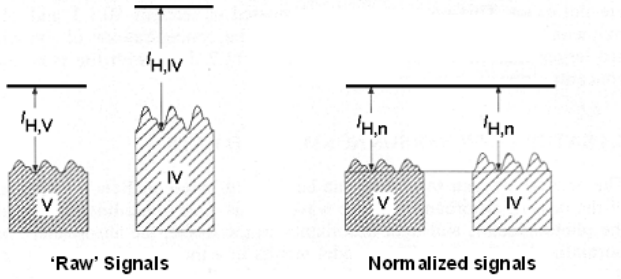

Fig. 4. Normalization of light signals intensities [33].

Light absorbance is thusly obtained in normalized form, by calculating the natural logarithm of normalized transmitted light intensity [33]. The total absorbance due only to alternated components is obtained by dividing the incident signal by the intensity of light when transmitted during diastole and calculating the total absorbance. The ratio *R* of those absorbances, normalized for the wavelengths λ_1=805nm and λ_2=1350nm, dependent only on the light absorbents present in arterial blood, is given by:

$$R = \frac{A_{t,1}}{A_{t,2}} = \frac{\ln\left(\frac{I_{L,1}}{I_{H,1}}\right)}{\ln\left(\frac{I_{L,2}}{I_{H,2}}\right)} \tag{8}$$

where $I_{L,1}$ and $I_{L,2}$ correspond to the minimum value of the signal transmitted during diastole for the wavelengths of 805nm and 1350nm, respectively, and $I_{H,1}$ and $I_{H,2}$ correspond to the maximum value of the signal transmitted during systole for the wavelengths of 805nm and 1350nm, respectively.

The incident light propagating through human tissue is not decomposed only in absorbed light and transmitted light, as proposed by the Beer Law. For some light components there are the phenomena of reflection and dispersion.

Skin surface, tissues, muscles, bone and specially blood cause dispersion of light, which increases the absorbance of light. Blood is not a homogeneous liquid and it is capable of non-linear absorbances such as the ones obtained when glucose concentration varies [38].

Due to the factors above, most of the equipment employing this measurement method use the R ratio, known as ratio of ratios or modulation ratio, which can be defined exactly by the equation 8, but which, due to deviations and imperfections in the setup of the measurement process, is normally approximated using the relationship:

$$R \approx \frac{AC_1 / DC_1}{AC_2 / DC_2} \tag{9}$$

where the AC component is the alternated variation from peak to valley of the cardiac frequency signal and the DC component is the average of all light intensity transmitted for all wavelengths used.

In order to relate the values calculated for the R ratio with the glucose concentration value C_G presented by the pulse glucometer, the equation for the theoretical calibration curve based on Beer Law may be modified as described by Mendelson and Kent [40], resulting in:

$$C_G = \frac{k_1 - k_2 R}{k_3 - k_4 R} \tag{10}$$

Another approximation for the mathematical representation of the calibration curve uses a polynomial such as the one found in several pulse oximeters [41], i.e.,

$$C_G = k_1 + k_2 R + k_3 R^2 \tag{11}$$

where the constants k_1, k_2, k_3 and k_4 are determined through calibration and clinical studies in order to obtain the best adjustment for the calibration curve.

To calculate the R value this study used the average of the R values for 12 consecutive cardiac cycles, generating an average delay of 6 cardiac cycles (approximately 6 seconds) in the presentation of the value estimated by the instrument, which proved acceptable for blood glucose measurements. The detection of a heartbeat in the tested instrument was performed using a real time algorithm to qualify oscillatory biological signals proposed by Navakatian et al. [39].

Accuracy (Arms), average deviation (B), standard deviation (SDR) and precision (Ps), as suggested by Severinghaus [21], were calculated for several conditions with the use of the following mathematical expressions:

$$Arms = \sqrt{\frac{\sum_{i=1}^{n} (G_i - Gr_i)^2}{n}} \tag{12}$$

$$B = \frac{\sum_{i=1}^{n} (G_i - Gr_i)}{n} \tag{13}$$

$$SDR = \sqrt{\frac{\sum_{i=1}^{n} (G_i - Gfit_i)^2}{n-2}} \quad (14)$$

$$Ps = \sqrt{\frac{\sum_{i=1}^{n} (G_i - Gr_i - B)^2}{n-1}} \quad (15)$$

where n is the number of measurement pairs used, G_i is the i^{th} blood glucose level value estimated by the pulse glucometer hereby proposed, Gr_i is the i^{th} reference value presented by the commercial personal blood glucose level monitor of the "fingertip" type and $Gfit_i$ is the i^{th} blood glucose level value, adjusted with the polynomial curve.

The necessary tests to validate the proposed instrument are typically performed in a clinical environment. It is necessary to include in the demographic sample people from both genders, several different ages and skin pigmentation

A test with 20 human volunteers was performed in order to validate the proposed device. The glucometer performance was checked by comparing its readings with the blood glucose level values determined by a commercial blood glucose level monitor used as reference.

Twenty human volunteers, both male and female, aged 16 to 63, weighing 48 to 112 kg and belonging to different races were tested. The volunteers were oriented to maintain their regular eating habits, without carbohydrate restrictions for the 72 hours prior to the exam, to not exercise on the day of the exam, to not eat during the exam and to fast for 8 to 12 hours before the exam. The test protocol decreed that, if the blood glucose level after fasting was measured above 140 mg/dl, the test would not be performed; such did not happen.

The test was performed by monitoring the blood glucose level (glucose concentration in the blood) for 3 continuous hours with the proposed device and by taking nine blood glucose level measurements using a commercial personal blood glucose level monitor of the "fingertip" type (ACCU-CHECK ADVANTAGE – Roche Diagnóstica Brasil). For each measurement taken with the commercial personal blood glucose level monitor it was necessary to puncture the finger to collect a small blood sample using a disposable lancet. Samples were collected after fasting and 15, 30, 45, 60, 90, 120, 150 and 180 minutes after the ingestion of 75 grams of glucose.

III. Presentation and Analysis of Results

All results presented refer to the twenty volunteers that were part of the clinical trial. A total of 180 measurements of blood glucose level values were used; the values recorded were the ones referring to the reading on the commercial blood glucose level monitor and the R values presented by the proposed instrument, with nine measurements taken for each volunteer.

Table I presents the data collected from a volunteer (jctbm0910) to exemplify the process.

TABLE I
DATA COLLECTED FROM VOLUNTEER JCTBM0910

Measurement	Measurement instant (hour: minute)	Commercial glucometer (mg/dl)	R Value Proposed Device
1	0:00	110	5.1619
2	0:17	132	5.6912
3	0:31	179	6.4536
4	0:47	208	6.8087
5	1:09	211	7.2504
6	1:35	174	6.3811
7	2:02	159	6.3371
8	2:32	158	6.0635
9	3:01	128	5.6227

After collecting data from the 20 volunteers, a polynomial adjustment was made considering all data collected in order to determine the best calibration curve R for this given measurement group. The curve presented in this section was adjusted with the polyfit function of the MATLAB software and a second degree polynomial was used to adjust the R curve, as is commonly used for pulse oximeters and which is also the best option for the developed glucometer.

Considering all volunteers, the adjusted polynomial which best represented the R curve was given by:

$$C_G = -55.6606 + 16.9413R + 2.7869R^2 \quad (16)$$

with an accuracy of ± 10.33 mg/dl and a precision of ± 10.40 mg/dl.

Table II presents the accuracy (Arms), the average deviation (B), the standard deviation (SDR) and the precision (Ps) of the measurement pairs collected from all volunteers with the proposed pulse glucometer as a function of the measurements taken with the commercial blood glucose level monitor. Calculations were performed according to the equations (12) to (15).

TABLE II
CALCULATIONS OF ACCURACY (ARMS), AVERAGE DEVIATION (B), STANDARD DEVIATION (SDR) AND PRECISION (PS) OF THE MEASUREMENT PAIRS COLLECTED FROM THE TESTED PULSE GLUCOMETER AS A FUNCTION OF THE MEASUREMENTS TAKEN WITH THE COMMERCIAL GLUCOMETER FOR SEVERAL VOLUNTEERS

Volunteers	B (mg/dl)	Arms (mg/dl)	SDR (mg/dl)	P_S (mg/dl)
ess1008	-2.0770	5.4912	7.4178	5.3916
rabs1308	3.3698	11.7406	15.6291	11.9288
seas1408	2.0996	8.9283	11.3226	9.2043
mcmm1708	-3.6411	16.6316	21.2093	17.2126
cc2008	3.1095	9.7693	12.0589	9.8230
mlc0309	3.0653	10.0404	13.5804	10.1410
css0809	1.8288	4.5300	6.6921	4.3959
daor1509	-2.1906	5.6842	7.9534	5.5633
etk1609	-1.6115	5.0367	9.1994	5.0614
esf1709	2.1662	17.2033	19.8997	18.1017
mrn1809	-1,1893	4.7615	4.9150	4.8903
fhm2109	8.6797	21.3250	29.9100	20.6603

sam3009	-1.3629	6.0252	7.9060	6.2250
mvbg0810	-0.6121	4.7760	7.6860	5.0239
jctbm0910	-4.7635	8.3891	13.8248	7.3244
rcj1310	-2.1158	7.3316	14.0709	7.4455
aga1410	-0.4889	20.3475	24.9199	21.5755
gsm1510	0.5984	14.2425	16.0635	15.0931
fr1610	0.1223	14.9896	17.9013	15.8983
cam1910	-3.3095	5.9212	12.9971	5.2079

Afterwards the data from the tested glucometer were compared to the data from the commercial glucometer in order to verify the possibility of obtaining a linear curve with an angular coefficient near one unit (identity curve).

Fig. 5 and Fig. 6 present the polynomial adjustment for the R curve and the identity curve, when comparing the tested glucometer with the commercial glucometer, both considering all volunteers.

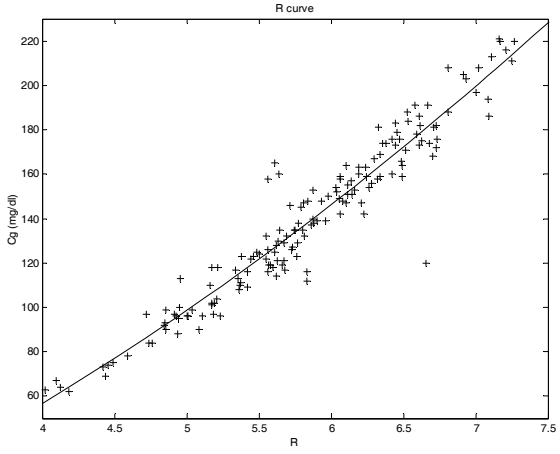

Fig. 5. R Curve.

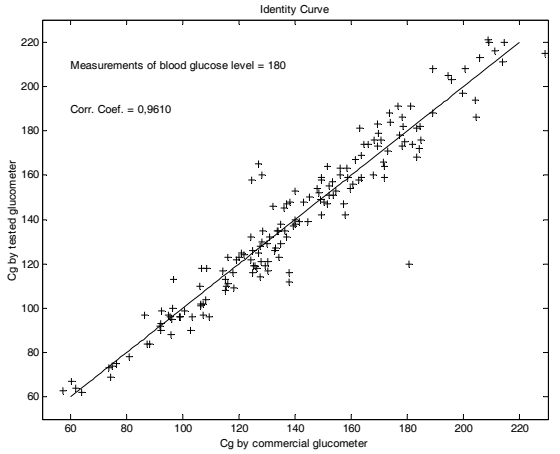

Fig. 6. Identity Curve.

IV. Conclusions and Perspectives

The proposed device, developed for continuous non-invasive monitoring of glucose concentration on arterial blood adopting the same method used in pulse oximetry presented good results (accuracy of ± 10.33 mg/dl and precision of ± 10.40 mg/dl) when compared to blood glucose level monitors of the "fingertip" type, which present readings with an accuracy in the magnitude of 15 mg/dl for the range of measurements used [43], enough for the daily monitoring of diabetes patients.

An extensive search of national and international patents and articles was conducted, allowing the conclusion that there is no publication or patent deposited of the measurement method used in this work. Therefore, an international patent was requested by the authors.

The natural sequence after this work is the development of another study using different wavelengths, in the range of 1450nm or 1900nm, where there is a greater absorption of glucose molecules [36], and also using components with better light power than the ones commercially available when this work was performed, since there is great attenuation in human tissues for those wavelengths.

Several other pairs of pulse glucometers and LEDs can also be used in order to increase the number of measurements taken and also in order to capture the variations relative to the electronic components used to build the proposed device, as well as variations in wavelength and sensor temperature.

Future perspectives involve performing another clinical trial, this time in a clinical analysis laboratory, where a greater number of volunteers and a wider range of blood glucose levels would be available.

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