Non-Invasive Blood Glucose Sensor: A Feasibility Study

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***Abstract*— Diabetes is a chronic disease characterized by abnormal blood glucose levels which has short and long term complications. Management of diabetes relies on a regular control of blood glucose levels, commonly measured with invasive sensors, which are painful and cause patient discomfort. Scientific community is trying to develop non-invasive monitoring sensors to measure blood glucose continuously. Whereas previous work are focused on single methods and techniques, we present hereby a feasibility study of a non-invasive sensor integrating three different types of techniques: electromagnetic, acoustic speed and near infra-red spectroscopy. Our prototype is subject to different sources of bias, however, the cross-compensation of these three techniques can minimize the low performance of single-technique approaches. The results are promising and show the potential of using combined techniques for non-invasive blood glucose measurement.**

I. INTRODUCTION

Diabetes Mellitus (DM) is defined as a set of metabolic disorders caused by a dysfunction of the pancreas [1]. There are two predominant types of DM: type 1 diabetes, originated by an impaired insulin secretion; and type 2 diabetes, which is due to abnormalities in insulin metabolism [1]. According to the World Health Organization, the global prevalence of diabetes has doubled, from 4.7% to 8.5% [2], and estimate that it will increase in the next decades [3]. Diabetes is one of the top leading causes of mortality and disability and imposes imposes a large economic burden [4].

Type 1 and type 2 DM are chronic diseases, in which maintaining adequate blood glucose levels is the central part of the treatment strategy [1]. Monitoring blood glucose is different depending on the type of diabetes: patients with type 1 DM need exogenous insulin and intensive monitoring of blood glucose, unlike type 2 diabetes, in which the control is less intensive (although periodic).

The sensors used for measuring the level of blood glucose can be classified into three categories: invasive, non-invasive and minimally invasive. Invasive sensors are defined as those that create a break in the blood vessels or capillary and make a contact beyond a natural or artificial orifice [5]. These type of sensors are widely accepted and clinically endorsed as regards of the accuracy they yield. However, to perform the measurement they require altering the integrity of the tissues and, therefore, may cause discomfort to the user [6]. The most common type of invasive measurement is based on a lancet, a reactive strip and a blood sample. The main drawback is that it does not allow a continuous measurement of the blood glucose, being able to produce hyper or undetected hypoglycemia. Its main advantage is that the measurement of glucose from blood samples is the most accurate method that exists, since the concentration of this substance in the blood is higher than in other human body fluids [7]. The measurement of glucose in these sensors is based on an enzymatic reaction in which the glucose oxidase in the test strip catalyzes the oxidation of the glucose present in the blood sample, in a reaction that generates a current proportional to the glucose concentration [8].

Minimally invasive sensors do not brake the blood vessels but from other tissues with blood irrigation and interstitial spaces. These sensors use a biodegradable catheter which should be placed with a special needle, and make the measurement from the mucose or internal cavity of the body.

Currently there are different minimally invasive and non-invasive methods that would allow the measurement of glucose level (www.medica-tradefair.com/). Some examples are the micro-pore technology [9], optical methods [10], electromagnetic and ultrasonic methods. Non-invasive blood glucose sensors are currently under development specifically in the application of absorption and transmission spectroscopy with a wavelength between 600 and 1000 nm by four LEDs. [11]. However, invasive sensors continue to be used today, most of them based on lancets and blood samples.

The purpose of the work reported in this paper is to investigate the clinical and technical fundamentals that enable a non-invasive measure of blood glucose. We discuss its advantages and possible disadvantages to propose a prototype of a non-invasive blood glucose sensor that integrates different sensing technologies.

II. MATERIALS AND METHODS

A. Fundamentals for non-invasive blood glucose monitoring

Changes in blood glucose concentration result in a flow of sodium and potassium ions in the cell compartment and the blood flow, and therefore a change in water concentration. This response to variations in the glucose level triggers changes at macroscopic level, reflected in a change in the electrical properties, acoustic impedance, thermal transfer and optics [12].

B. Bioelectrical properties

The interruption of the trans-membrane electrolyte balance produced by a glucose-induced liquid exchange alters the membrane potential. These variations correspond to the active D-glucose enantiomer which affect both the permeability

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and the conductivity of cell membranes. Therefore, the transport of both ions and water induced by glucose through the membrane produces changes in intra/extra-cellular electrical properties. These alterations are reflected in the changes in tissue impedance according to Figure 1, which is equivalent to a high impedance consisting of a resistance in parallel with a capacitor. This value is high since the epidermis and dermis are strongly insulating tissues.

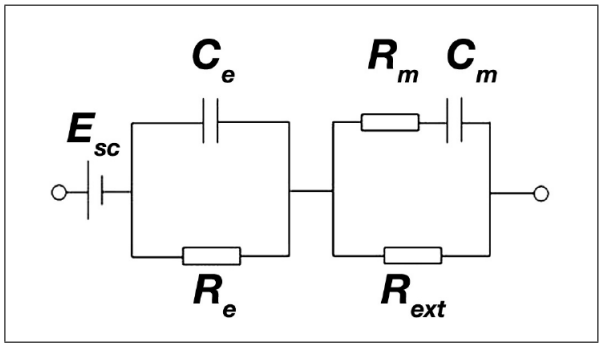

Fig. 1. Equivalent circuit of the epidermis and the underlying tissue.Esc, Ce, Re, Rm, Cm and Rext denote surface potential of the skin, epidermal capacitance, epidermal resistance, capacitance of the tissue cell membrane, resistance of the tissue cell membrane and extracellular resistance, respectively. Source: [12]

Shift of electrical properties are due to a transport of ions and water through the cell membrane induced by the variation of glucose. This directly affects the dielectric properties, which in turn affects the impedance of the tissue. An electromagnetic channel with a self-oscillating circuit can capture changes in skin impedance. Thus, the electromagnetic signal measured by this circuit will be directly related to the variation of glucose, and what will be offered will be different frequencies depending on this concentration [13].

C. Acoustic speed propagation

The speed of acoustic transmission in soft tissues depends both on the compressibility, which is determined by intermolecular forces, and on the density of the medium, according to Equation 1. expression:

$$c = [(1/\beta\rho)]^{(1/2)} \tag{1}$$

The rupture of the structure of the water by means of the hydrogen in glucose molecules cause the water to be less united and form a less compact structure [14]. That is, changes in glucose concentration translate into changes in the compressibility and density of water and therefore a change in the speed of acoustic transmission.

Changes in glucose concentration can be measured indirectly by measuring the speed of a sound through tissue [12]. Speed of sound has a linear relationship with glucose concentration, shortening the propagation time.

The measurement circuit employed consists of an ultrasound probe faced to the tissue. The continuous ultrasonic wave produced by the emitter travels through the tissue with a characteristic velocity. The receiver will detect a phase shift () which will be related to level of glucose present in the tissue (Equation 2). Where f is the frequency of the emitted signal, d the distance between the emitter and the receiver and the phase shift

$$V = ((f * d) * 2\pi)/\Delta\phi \tag{2}$$

This signal will be altered by the ambient temperature and the relative temperature of the tissue where the sensor is placed, therefore it will need a correction factor.

D. Near infra-red spectroscopy

Water is the main component that interacts with Near Infra-Red (NIR) radiation in the human body. Changes in the absorption and dispersion of light in water will vary depending on the presence of glucose molecules [15].

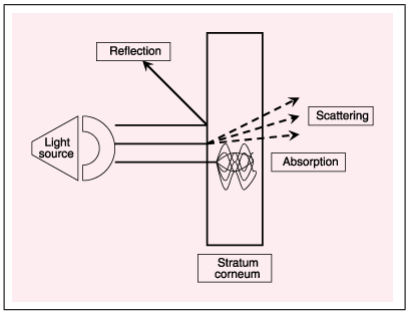

Fig. 2. Interaction of light with the skin and the different emissions it produces. [15]

The wavelength used in NIR spectroscopy ranges from 750 to 2500 nm, and the error of measurement depends of the tissue. Correlations between glucose and the level of NIR absorbed depend on the wavelengths used and therefore for each wavelength there will be a determined error (RMSECV) and a model which requires validation have to be validated [16]. This technique has some limitations since it is affected by changes in body temperature, blood pressure, skin hydration and triglyceride and albumin concentrations. Besides, it is difficult to differentiate between the contribution due to the blood and the contribution to the interstitial fluid.

III. Results

A. Proposal of a non-invasive sensor

In the present work we propose a non-invasive device that allows the monitoring of glucose levels continuously with a measurement as close as possible to those offered by current invasive methods. Given that the aforementioned technologies present errors of glucose estimation, a sensor based exclusively on one of these technologies would not be valid for the measurement of blood glucose. For this, the 3 technologies described above are be combined in a single device.

To minimize the detection error and the impact of the various perturbations that affect each technologies we propose to measure different tissue parameters that are affected by the same change in glucose concentration. Therefore, each method is indicative of blood glucose level, but is limited by the impact of interfering factors due to lack of

specificity. The integration of three modes for the evaluation of the glucose level allows more precise readings, while an error introduced by one modality can be corrected by the other two. In addition, the proposed techniques are chosen since they are based on different physical properties of the individual, that is, the variables monitored by the measurement channels are independent and allow to receive information with sufficient resolution to work with. The use of multiple sensors is promising, since this integration contributes to increase the signal-to-noise ratio. The use of multiple sensors facilitates the determination of the contact quality of the sensors, as well as the compensation and correction of bias (such as temperature), and gives an account of the validity of the measured parameters.

A Clarke error grid (CEG) will be used to evaluate the errors made by this novel device. CEG is a statistical analysis that evaluates the differences between the results of our device and the established blood glucose reference method.

B. Calibration

In order to validate this device, it requires calibration and validation, which certifies that the non-invasive measures that are being carried out actually correspond to reality.

In relation to the calibration, this is done so that the effect of certain variables not related to the study, but that do affect the development of the same, will be attenuated. These factors, due to the variability between people, such as tissue density, sweat, etc., will be eliminated after calibration. The process consists in correlating the data of the invasive measure taken from the finger capillary blood with N sequential measurements with the non-invasive instrument, generating a calibration curve that is unique to each individual. These measurements are made over a certain time, causing the subject to consume a certain amount of sugars so that the glycemia increases and the instrument is able to detect increases and decreases in blood glucose.

$$BGreading = a + bdata(n, g, T) \tag{3}$$

The model that follows this calibration is shown in Equation 3. That is, the data collected by the sensor would be multiplied by a constant b and a constant a would be added, these data being unique for each individual, since they reflect the particularities and variability of each one of them. The data introduced have as variables the intrinsic noise (n), the blood glucose level measured by the non-invasive device (g) and the temperature (T).

After verification of the position of the device, using the distance reference established during the calibration, the measurement of the variables begins. Each measurement channel produces several outputs, on which a three-stage signal processing is applied: signal validation and outlier detection, temperature compensation and temperature correction. In summary, our device would yield results such as those observed in Figure 20 and, depending on the weights assigned during the calibration, technologies or others will be taken into account to a greater extent in order to give a result as reliable as possible.

Fig. 3. Example of the wired prototype of the sensor, placed in the ear lobe

C. Prototype

Once the steps of validation, calibration and operation have been explained, we propose a design that incorporates the different sensing techniques. Ear lobe correlated with blood glucose despite having a small delay. As commented by Harman-Boehm et al. acoustic and electromagnetic technologies work correctly in the lobe of the ear [12]. This is why it has been decided that our continuous non-invasive measuring device should be placed in the ear lobe. Since it is relatively comfortable for the patient, unlike a device located in the labial area, and has good predicted results. The design of our device will follow the following prototype (Figure Z)

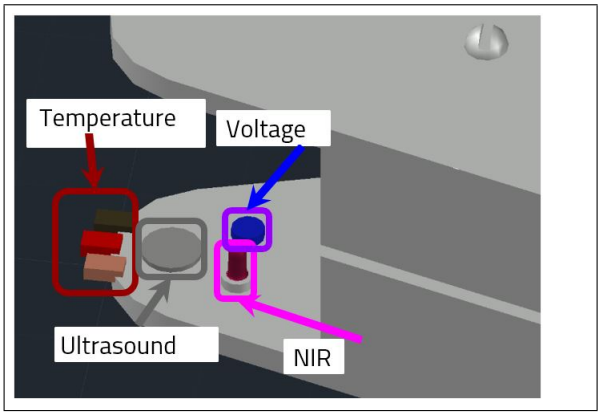

Fig. 4. Set up schema of the built in sensors for the four magnitudes

As has been discussed throughout the work, this prototype incorporates four measurement technologies (Figure 4). The lobe of the patient's ear will be placed in the space in the sensor, so that the thermal sensors can determine the different temperatures, the NIR radiation and the ultrasound can cross the lobe and the electromagnetic signal at a certain frequency

can reach the receiver.

IV. Discussion

With the present work we have tried to emphasize the need to develop a non-invasive glucose measuring device. This would not only improve the quality of life of patients who must currently use the lancet on a daily basis, but would possibly achieve a more continuous monitoring and thus avoid hiccups and hyperglycemia not detected in time.

With the existing technology, it is possible to combine several glucose measurements based on non-invasive physical properties, estimating each one of them the approximate glucose concentration and performing a weighted averaging to obtain a value that is as close as possible to that which is I would get by measuring directly in blood. However, in all the techniques developed there are limitations due to physical, chemical and environmental factors. To reduce the error of these factors and artifacts it would be necessary to perform a calibration and a validation of the models to ensure that the measurements are correct, as well as a greater sensitivity of the measuring instruments.

It is feasible to develop a non-invasive device that allows the measurement of glucose, although there are still many handicaps that must be faced in the future. Among them, that is fast, reliable and does not require the continuous attention of the user, in addition to other less critical requirements, such as comfort and aesthetics.

The proposed device has two measurable disturbances that we must take into account when making the measure. One of them is the temperature of the fabric that is between the two measuring plates: given that the impedance is directly proportional to the temperature of the fabric itself, we must take care of measuring its temperature and subtract from the signal the variations due to this, so that we stay exclusively with the variations dependent on the level of glucose. Another disturbance is due to the ambient temperature, which affects both the properties of the tissue and those of the electromagnetic sensor (for example, the parasitic capacity of the electrodes). Glucose variations affect the characteristics of heat transfer through changes in conductivity, density and specific heat, this is due to changes in water and electrolytes in it [12].

Therefore, it is possible to evaluate glucose indirectly by measuring the characteristics of the heat transfer in response to a specific amount of energy delivered to the tissue during a given period of time. However, the HTA process is also affected by the speed of the blood and the generation of metabolic heat. Therefore, it may also be sensitive to changes in perfusion and circulatory problems, which result from the complications of diabetes, as well as the level of physical activity of the patient before the measurement. It is for this reason that our device evaluates glucose through various parameters to prevent interferences inherent in the human body

The intensity of the reflected light signal varies according to the chemical environment: the influence of the dissolved salts and the temperature in the NIR spectra of an aqueous system is considerable. The normal proportion of glucose in blood and tissue is only 0.1% in water, so the spectral variation due to this glucose concentration is extremely small. This makes the evaluation of the spectrum obtained complicated due to the interference of several factors: water absorbs a large part of the radiation, and because glucose is so abundant, it does not generate significant changes in the spectrum.

Another possible field of future work in this branch would be the investigation of other biofluids and their relationship with blood glucose such as sweat, saliva and urine [17]. It is therefore a field in which although there is literature and progress discovered to date, there is still work to be done.

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