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Blood Glucose Detection Using 3-LEDs: Analytical Model

Detecção de glicose no sangue usando 3 LEDs: modelo analítico

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Abstract

Calibration of non-invasive blood glucose measuring devices have an important role in the routine of people with diabetes. Continuous monitoring is one of the most efficient manner to control the disease. Besides the errors associated with the user, the calibration of such devices is the key point for obtaining reliable data. Researchers have failed to correlate the 2 near-infrared-light wavelength response from skin with the blood glucose level and then use it for diagnosing both upper and lower glycaemia status. The aim of this article is to purpose a mathematical model for calculating the blood glucose level using 3-LEDs with different wavelengths. It is presented and demonstrated all equations involved by using the theory of absorption of light by photoplethysmography. The final proposed equation can be calculated without using prior data obtained from patient. It can be concluded that it is possible to reduce the necessity of using calibration processes before acquiring data by a non-invasive device.

Keywords: Blood Glucose; Photoplethysmography; NIR; 3-LED Modeling.

Resumo

A calibração de dispositivos não invasivos de medição de glicose no sangue tem um papel importante na rotina das pessoas com diabetes. O monitoramento contínuo é uma das formas mais eficientes de controle da doença. Além dos erros associados ao usuário, a calibração de tais dispositivos é o ponto chave para a obtenção de dados confiáveis. Os pesquisadores não conseguiram correlacionar a resposta de 2 comprimento de onda de luz infravermelha próximas da pele com o nível de glicose no sangue e, em seguida, usá-lo para diagnosticar o estado de glicemia superior e inferior. O objetivo deste artigo é propor um modelo matemático para o cálculo do nível de glicose no sangue usando 3-LEDs com diferentes comprimentos de onda. São apresentadas e demonstradas todas as equações envolvidas com o uso da teoria de absorção de luz por fotopletismografia. A equação final proposta pode ser calculada sem o uso de dados anteriores obtidos do paciente. Pode-se concluir que é possível reduzir a necessidade de utilização de processos de calibração antes da aquisição de dados por um dispositivo não invasivo.

Palavras-chave: *Glicose no sangue; Fotopletismografia; NIR; Modelagem de 3 LEDs.*

1. Introduction

Calibration of non-invasive glucose measuring devices can be done in two ways. One is through analytical calibration, which consists of a set of operations that establishes, under specified conditions, the relationship between the values indicated by a measuring instrument and the corresponding values of the quantities established by standards. For non-invasive glucose measurement devices, there are numerous sources of error that can affect the measurement, which need to be eliminated or compensated by a calibration method. However, not all sources of errors can be incorporated in the calibration, such as positioning of the detector, effect of temperature and cardiac pulse, movement, mechanical pressure of the test device, hydration status, sweat, blood volume and alteration of the hematocrit (1).

Several tissue simulators have been proposed as calibration systems. Some are suspensions of lipids or polystyrene particles in solutions with different concentrations of glucose. Others propose a phantom solution containing fat and glucose used to mimic the absorption of glucose into the tissue over a wave range of 2000nm to 2500nm (2). The development of tissue simulators as analytical standards for the determination of non-invasive glucose measurement in tissue is still a barrier to be overcome and that would bring great benefit to the development of the non-invasive methodology. therefore, a non-invasive device that is analytically calibrated can be considered universally calibrated, that is, it can be used with any patient.

Another way of calibrating non-invasive devices is through clinical calibrations, they are performed with the individual fasting at intervals of time during a meal tolerance test or in a glucose fixation procedure. These methods provide a concentration range in which the glucose signal can be monitored. Data from an OGTT (Oral Glucose Tolerance Test) can be used to establish a non-invasive glucose measurement device response as the subject's glucose concentration is changing. This type of calibration results in the incorporation of physiological effects unrelated to glucose and leads to a calibration correlation that is unique to the tested individual. This calibration curve may need to be updated periodically through an invasive test.

The idea of proposing a pulse glucometer based on the infrared spectroscopy technique has already been validated in (3), using the same principles of pulse oximeters. However, this work, like so many others, uses curve adjustments to calibrate the device.

Due to the problematic picture presented by the calibration of non-invasive glucose measurement devices that use near infrared spectroscopy

techniques, this article suggests a pulse glucometer that uses three LEDs through a mathematical modeling based on the Lambert-Beer law and also in the optical technique of plethysmography to detect changes in volumes in the microvascular bed of the tissue. This should discard the need for calibration if the requirements of the physical and mathematical approximations that are presented below are met.

2. Methodology

The processes of interaction between the radiation field and a medium are known as extinction and emission. When the light interacts with the sample, the electromagnetic wave can also be scattered. In spreading, unlike the absorption process, there is no removal of energy from the radiation field, but its redirection. Both in the absorption process and in the scattering process, the luminous intensity decays after it passes through the medium. This decay is called light extinction. Therefore the extinction coefficient α is defined as a combination of the absorption coefficients α_{abs} and scattering α_{esp} of all the particles in the medium when light passes through it (4), mathematically:

$$\alpha = \alpha_{abs} + \alpha_{esp} \quad (1)$$

Light absorption, according to the Lambert-Beer law (1,3,4) can be expressed as

$$I = I_o e^{-\alpha l} \quad (2)$$

where l is the effective length of the path in the middle and α is the extinction coefficient.

The blood extinction coefficient can be written as a combination of the glucose extinction coefficient plus the extinction coefficient of the rest of the fluid,

$$\alpha = \alpha_g C_g + \alpha_f C_f \quad (3)$$

Where

$$C_g + C_f = 1 \quad (4)$$

where α_g and α_f are the glucose and fluid extinction coefficients, respectively, and C_g and C_f are the coefficients that represent their concentration in the blood composition. Therefore, equation 3 can be rewritten as

$$\alpha = \alpha_g C_g + \alpha_f (1 - C_g) \quad (5)$$

$$\alpha = C_g(\alpha_g - \alpha_f) + \alpha_f \quad (6)$$

Equation 2 can be written as follows

$$ln\ ln\left(\frac{I_o}{I}\right) = \alpha l \quad (7)$$

For small variations in light intensity $I_0 - I \ll I$, then

$$ln\ ln\left(\frac{I_o}{I}\right) \cong \frac{I_0 - I}{I} \quad (8)$$

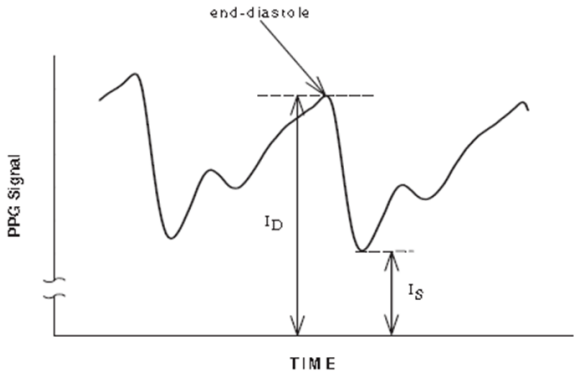
From the equations 7 and 8,

$$\frac{I_0 - I}{I} \cong \alpha l \quad (9)$$

Pulse oximetry is based on isolating the contribution of arterial blood to the absorption of light by photoplethysmography (PPG). The measurement of light absorption changes due to alterations in arterial blood volume induced by the heart. The PPG signal is shown in Figure 1. The intensity of transmitted light decreases during systole due to the increase in arterial blood volume during systole, when blood is ejected from the left ventricle into the peripheral vascular system.

The maximum and minimum values of the PPG signal ID and IS in Figure 1, respectively, are proportional to the irradiance of the light transmitted through the tissue in the final diastole and in the systole, when the blood volume in the tissue is minimal or maximum, respectively (5).

Figure 1 - The photoplethysmographic sign. Light transmission through the finger decreases during systole. ID and IS indicate the maximum and minimum values of light transmission during the cardiac period, respectively.



Source: Nitzan, M.; Engelberg, S. (2009).

In pulse oximetry, the transmitted light is measured in two wavelength, λ_1 and λ_2, and I_D and I_S are replaced by I_0 and I. A ratio R that isolates the contribution of the variation in blood volume due to heartbeat, taking into account the approximations given by the equation 9, is written as

$$R_{12} = \frac{\left(\frac{I_0 - I}{I}\right)_1}{\left(\frac{I_0 - I}{I}\right)_2} \quad (10)$$

where the indices 1 and 2 refer to the values of I_0 and I collected for wavelength λ_1 and λ_2 respectively. From the equations 9:

$$R_{12} = \frac{\alpha_1 l_1}{\alpha_2 l_2} \quad (11)$$

where α_1 is the blood extinction coefficient for wavelength λ_1, α_2 is the blood extinction coefficient for wavelength λ_2, l_1 and l_2 are the optical paths for the respective wavelengths λ_1 and λ_2.

From equation 6 it is possible to write the blood extinction coefficient for each wavelength, then

$$\alpha_1 = \alpha_{g1} C_{g1} + \alpha_{f1} C_{f1} \quad (12)$$

$$\alpha_2 = \alpha_{g2} C_{g2} + \alpha_{f2} C_{f2} \quad (13)$$

Replacing equations 12 and 13 in 11 and isolating the glucose concentration C_g:

$$C_g = \frac{\alpha_{f1} - \alpha_{f2} R_{12} \left(\frac{l_1}{l_2}\right)}{\alpha_{f2} R_{12} \left(\frac{l_1}{l_2}\right)(\alpha_{g2} - \alpha_{f2}) - (\alpha_{g1} - \alpha_{f1})} \quad (14)$$

The factor $\left(\frac{l_1}{l_2}\right)$ generally cannot be overlooked and, if not known, C_g cannot be derived from the measured value of R_{12}. In practice, the relationship between R and C_g is determined by calibrating each type of pulse glucometer sensor. R is measured in several individuals simultaneously with the in vitro measurement of C_g in arterial blood drawn using an invasive standard glucometer. For each person R and C_g in blood are measured at various values of C_g. The relationship between R and C_g is assumed how [3]:

$$C_g = \frac{a - bR}{c - dR} Cg \quad (15)$$

Or

$$C_g = a + bR + cR^2 \quad (16)$$

where the constants a, b, c and d are determined from the corresponding measured values of R and C_g. Equations 15 and 16 provide the necessary calibration for the derivation of C_g from the measured parameter R. Calibration for devices with two LED's assumes that $\left(\frac{l_1}{l_2}\right)$ does not change between different people and different physiological and clinical situations. The validity of this assumption is limited and deviations are probably the main source of the inaccuracy in the evaluation of C_g by the method implemented.

3. Results

As shown for LEDs with λ_1 and λ_2 wavelengths in equation 10, a third LED with λ_3 wavelength can be introduced:

$$R_{13} = \frac{\alpha_1 l_1}{\alpha_3 l_3} \quad (17)$$

where l_3 is optical paths for the third LED.

And from equation 6:

$$\alpha_3 = \alpha_{g3} C_{g3} + \alpha_{f3} C_{f3} \quad (18)$$

Now, replacing the equations 13 and 15 in 12:

$$C_g = \frac{\alpha_{f1} - \alpha_{f3} R_{13} \left(\frac{l_1}{l_3}\right)}{\alpha_{f3} R_{13} \left(\frac{l_1}{l_3}\right)(\alpha_{g3} - \alpha_{f3}) - (\alpha_{g1} - \alpha_{f1})} \quad (19)$$

R_{12} e R_{13} of equations 10 and 17 can be measured, and the extinction coefficients α_1 and α_2 for the three wavelengths can be obtained in the literature or even in text bench. However, to determine C_g, it is necessary to find $\left(\frac{l_1}{l_2}\right)$ and $\left(\frac{l_1}{l_3}\right)$.

The optical path l, as well as its standard deviation, the relationship between the wavelength and the distance between the light source and the detector increases with the scattering constant and decreases with the absorption constant. Since the dependence of scattering on the wavelength is smooth, the relationship between the path length l and the wavelength is also smooth in the spectral region where the extinction coefficients, since hemoglobin depends gently on the wavelength. If λ_1, λ_2 and λ_3. are chosen as three adjacent wavelengths in an appropriate infrared region, a linear relationship can be assumed between small changes in the path length l and small changes in λ wavelength (5):

$$l - l_0 = k(\lambda - \lambda_0) \quad (20)$$

Where k is a constant. In this way, you can write:

$$l_1 - l_2 = k(\lambda_1 - \lambda_2) \quad (21)$$

And

$$l_1 - l_3 = k(\lambda_1 - \lambda_3) \quad (22)$$

Dividing equation 21 by 22:

$$\frac{\lambda_1 - \lambda_2}{\lambda_1 - \lambda_3} = \frac{1 - \left(\frac{l_2}{l_1}\right)}{1 - \left(\frac{l_3}{l1}\right)} \quad (23)$$

Of the equations 16, 17 and 23 C_g can be determined without prior information about $\left(\frac{l_2}{l_1}\right)$ and $\left(\frac{l_3}{l_1}\right)$, since there are three equations in three unknowns : C_g, $\left(\frac{l_2}{l_1}\right)$ and $\left(\frac{l_3}{l_1}\right)$.

4. Discussions

As for the choice between measuring the absorption or spreading coefficient, the suggestion is to use the spreading coefficient. This is because the change in light absorption measured by α_{abs} may occur due to the increase in glucose concentration, where α_{abs} increases with the increase in glucose, or by decreasing water, where α_{abs} decreases with increasing glucose. However, several other parameters may be responsible for the decrease in water, since any other solute other than glucose, if increased, causes a kind of water displacement, such as hematocrits. Changes in temperature and hydration status also affect the water absorption bands and act as noise sources for a non-invasive glucose measurement.

The glucose absorption coefficient in the IR is much lower than that of water. Its magnitude is too small to allow direct measurements of absorption at wavelengths below $1400\ nm$. The attenuation of light in this wavelength range in a certain part of the body, which may be a finger, varies in the range of 3 to 4 absorbance units, while the change caused by $5\ mmol/L$ in the glucose concentration is approximately 10^{-5} absorbance units (1).

While, for the intensity of the light spread over the tissue, it is altered due to the variation of the glucose concentration. A reduced scattering coefficient, $\alpha'_{esp} = \alpha_{esp}(1-g)$ where g is the anisotropic factor, of a tissue can be written as a function $\alpha'_{esp} = f(\rho, a, n_{cells}/n_{medium})$, where ρ is the numerical density of the dispersing cells in the observation volume, a is the diameter of the cells, n_{cells} is the refractive index of the cell and n_{medium} is the refractive index of the interstitial fluid (6).

Changes in n_{medium} can be caused by any change in the total concentration of solutes in the blood and in the interstitial fluid. (1) analyzes the variation of the water refraction index, based on (7), showing the change in n_{water} caused by various metabolic factors. It is evident that during hyperglycemic conditions, the concentration of glucose changes rapidly, while other concentrations of solutes change at a slower rate. Thus, it is possible to relate α'_{esp} to changes in glucose concentration in a short period of time.

However, as the temperature increases, the water decreases, characterizing dehydration, this affects n_{cells}/n_{medium} in the tissue (7) and presents a source of error in the scattering measurements. It is already confirmed that values of α'_{esp} decrease with increasing concentrations of glucose (8) and other sugars in in vitro tissue simulations due to their effect on n_{medium} (9).

5. Conclusion

The mathematical model presented has the potential to rule out the need for calibration for non-invasive blood glucose measurement devices if the boundary conditions and applied engineering technology are met. This would be of great applicability for patients with Diabetes, as it will avoid the need for frequent calibrations of monitoring devices and also a reduction in measurement errors due to the solution of errors associated with calibration.

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