

Article

Analytical Model for Blood Glucose Detection using Electrical Impedance Spectroscopy

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Abstract: Pathogens and adulterants in human feeding consumables can be readily identified according to their electrical properties. Electrical bioimpedance analysis (BIA) has been widely used for body contents characterization, such as blood, urine, lactate and sweat. If the blood glucose concentration alters the electrical properties of the blood medium, then the impedance spectrum obtained by BIA can be used to measure glycemia. In some applications, artificial neural networks allows the correlation of these parameters (impedance and glucose concentration) by means of symbolic and statistical rules. According to our literature review, there is any physical model that allows the interpretation of the relationship between blood's electrical properties, obtained by BIA, and the concentration of glucose in the blood plasma. This article proposes a simplified physical model for blood electrical conductivity as a function of glucose concentration, based on Bruggeman's effective medium theory. The equations of this model were obtained considering an insulating phase distribution diffused in a conductive matrix, in which red blood cells are represented by macroscopic insulating nuclei and glucose molecules by microscopic insulating particles. The impedance spectrum for different glucose concentrations (4.0 to 6.8 mmol/L) in a blood sample, published by Kamat Bagul (2014), were compared with the proposed model. The results showed a significant correlation with the experimental data, showing a maximum error of 5.2%. The proposed model might be useful in the design of noninvasive blood glucose monitoring systems.

Keywords: Blood Glucose; Analytical Model; Impedance Spectroscopy; Noninvasive Monitoring.)

1. Introduction

Glucose is the main energy conveyor carbohydrate in most of the animals. In human blood, glucose concentrations should be around 89 mg/dL to 125 mg/dL [1] for healthy conditions. Any value that resides outside this range can be hazardous, causing a well known disease, diabetes. Nowadays, many monitoring techniques can be found in the literature which are specially designed to assist people with diabetes [2].

Most of the reliable diabetes monitoring systems are invasive, that is, require a blood sample in order to measure the glucose concentration. Unfortunately, these methods can cause pain, be expensive in the long run and be prone to causing infections by opening wounds in the patient skin [3] For that reason, developing non invasive devices for accurate and reliable measure of blood glucose concentration is a remarkable topic in the specialized literature [4]. These devices can improve health quality of people with diabetes, allowing continuous monitoring of glucose levels and leading to precise medication administration.

There are glucometers based on radio wave transmission. However, the high frequencies necessary to reduce skin effects places difficulties in these measuring systems. Photoplethysmography is a method that relies upon infrared emission, where the absorption pattern is used to estimate glucose concentration. Unfortunately, this method requires a precise tracking of the heart rate by a second measuring system. Besides that, an electrode pair must be placed on the skin in order to accurately measure tissue conductivity and permeability [5][6].

BIA has been successfully applied in the non invasive prognosis and characterization of living tissues. It consists of electrode pairs placed on a patient's skin. A sinusoidal current is injected by a pair of electrode, while the second pair measures the voltage drop across the sample under study. The tissue impedance can be estimated and, with help of analytical models for conduction, intrinsic parameters are calculated in order to assist medical prognosis [7].

The major drawback in these BIA sensors are their complexity and development expensiveness [8]. Because of that, [5] proposes a reliable and low cost method in which results were compared with [8], showing equivalent precision with a clear relationship between glucose concentrations and tissue impedance spectra.

Advances in electrical approaches are important for accurate detection, but also analytical models have been proven to be useful for blood investigations. There are models that analytically correlate blood properties with electrical parameters [3][9][10]. One of such model establishes a correlation between blood and its mechanical properties, like viscosity, and electrical conductivity [9]. The results show reasonable agreement with experimental data, for both diabetic and healthy blood, concluding that BIA can be used to investigate blood micro structure. The study presented by [10] brings a detailed model that includes several blood parameters and their relation to electrical impedance. However, these studies cannot establish a clear connection between glucose concentration, excitation frequency, and electrical blood conductivity. However, experimental data shows correlation of these parameters [5][8][11].

An alternative approach to the problem of estimating glucose levels is by using statistical and artificial neural networks (ANN). In these frameworks, an algorithm searches for a relationship between several input parameters and a target prediction: the blood glucose level. It is highly recommended that a ANN be trained with large experimental databases, [12][13] so it can lead to a proper convergence at its output. Once extensively trained and calibrated, ANN can be applied to estimate glucose levels with a given input data from outside the training set [14].

The main problem in any ANN comes from its output nature, that is, a statistical prediction [15]. ANN gives an output summed with an inference error, that comes from its mathematical structure. The larger the training databases the better, because in order to reduce inference error it is necessary to hold the input parameters in the training data neighborhood. Contrariwise, a mathematical model that properly describes the phenomena gives a prediction that only relies upon measuring precision. Instead of the inference error, this approach carries a propagation error that arises only from the measuring methodology.

Regardless of its output prediction, ANN poses problems in the nature interpretation of the input data. In fact, the physical relationship between parameters are buried in the deep learning layers of ANN. If the relative rate of a parameter is required, then mathematical models are able to offer estimations by using straightforward algebraic equations. Additionally, ANN requires a new set of training data that depends upon a complete different experimental methodology in search for such estimation. Therefore, ANN have less flexibility into comparison to mathematical models when a deep study of phenomena is required. From a summarized perspective, to increase precision on the output of an ANN it is necessary to enlarge the training databases, both quantitatively and qualitatively [16]. Mathematical models only require an increase in experimental precision in order to reduce the propagated error.

The study performed here applies the Effective Medium Theory (EMT) to describe the phenomena of glucose levels correlated to the electrical blood conductivity. The study done by [17] presents Bruggeman's equations as an appropriate model for blood conduction, where the space's non homogeneity distribution is taken into account. Thus, the volume conductor is modelled by both insulating and conductive phases. The red cells and glucose molecules compose the insulating phase, while blood plasma the conductive one.

Since first proposed by Bruggeman and Landauer [17], EMT has been the main framework in many applications where macroscopically composed medium is the object under study [18][19][20][21][22].

EMT poses important technological applications like for percolation theory, employed for the monitoring and the simulation of oil reservoirs [23]. Another example deals with the analysis of carbon nanotubes conductivity, which is a material that might increase performance of integrated circuits [24].

The focus of this article is to investigate the Bruggeman's effective medium theory by developing and proposing a simplified physical model for blood electrical conductivity as a function of glucose concentration.

2. Materials and Methods

The EMT describes composite materials resistivity as a function of the relative phase concentration, shape and distribution gradient. It is supposed that each ellipsoidal insulating grain is completely immersed in a conducting medium with known resistivity [25]. Figure 1 shows one randomly insulating grain distributions in a conducting medium [26].

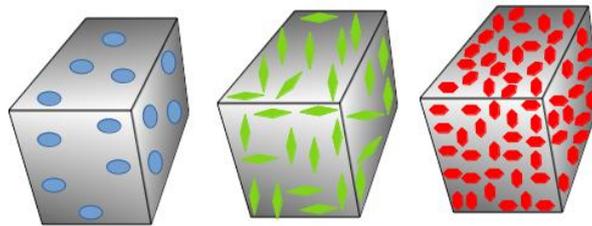


Figure 1. Representation of random insulating grain distributions in a conducting medium.

The Bruggeman's equations for asymmetric mediums, considering spherical grain inclusions, are:

$$\frac{(\sigma_m - \sigma_l)^3}{\sigma_m} = (1 - k)^3 \frac{(\sigma_h - \sigma_l)^3}{\sigma_h}, \quad (1)$$

$$\frac{(\sigma_m - \sigma_l)^3}{\sigma_m} = (1 - \phi)^3 \frac{(\sigma_l - \sigma_h)^3}{\sigma_l}. \quad (2)$$

where σ_m is the medium conductivity which contains two phases: a high conductivity material labeled σ_h , and a low conductivity one (σ_l). The volumetric fraction of the high conductivity phase is ϕ , and k for the low one. This definition implies that $\phi = (1 - k)$.

For the proposed model, σ_m should be considered the whole blood conductivity, σ_h as plasma conductivity, and σ_l for red cells conductivity. The volumetric fraction ϕ of the high conductivity phase is related to plasma volume, k is related to red blood cells volume.

In [17], the equation (1) represents a structure in which there is an insulating core submerged in a conductive medium with other smaller non conductive particles. Consequently, equation (1) is suitable for the required model, where the insulating core represents the red blood cells and glucose molecules the non conductive particles.

Considering a first approximation, σ_l can be taken zero because red cells are insulating in the proposed model. This hypothesis applied in equation (1) implies that:

$$\sigma_m = (1 - k)^{\frac{3}{2}} \sigma_h. \quad (3)$$

It should be considered that blood vessels are represented by perfect cylinders with homogeneous conductivity. Therefore, at a constant temperature, the second Ohms' law can be applied to give:

$$R = \frac{L\rho}{A} \quad (4)$$

where ρ is the blood resistivity, R is the vessel resistance, L and A are the length and traversal section area of the vessel, respectively. Combining equations (3) and (4) and considering $\rho = \rho_m = \frac{1}{\sigma_m}$, then equation (4) can be redefined by:

$$R = \frac{L}{A\sigma_h} \frac{1}{(1-k)^{\frac{3}{2}}}. \quad (5)$$

The impedance Z is the opposition to an alternate current flow. By standard, Z is highly sensitive to frequency for any living tissues. usually, the real part of the impedance is associated with water content, while the imaginary part with capacitive effects of cell membranes [27]. The modulus of the impedance can be given by:

$$|Z| = \sqrt{R^2 + \chi^2}. \quad (6)$$

While the reactance part by:

$$\chi = \frac{1}{2\pi fC} \quad (7)$$

where C is the total equivalent capacitance of sample under study and f the frequency excitation.

According to the classical electromagnetism theory, when charges are submitted to a potential variation then a current flow without physical displacement of charge in a cross section between potential boundary is established. This phenomenon leads to a "resistance" associated with a capacitance, so that:

$$C = \frac{\varepsilon\rho}{R}, \quad (8)$$

where ε is the medium electrical permittivity.

Combining equations (5) and (8), and rewriting $\rho = \rho_m = \frac{1}{\sigma_m}$, then equation (8) can be rewritten as:

$$C = \frac{A\varepsilon}{L}. \quad (9)$$

This last implies that the reactance by equation (7) can be written as:

$$\chi = \frac{L}{2A\pi\varepsilon f}. \quad (10)$$

The electrical impedance can be rewritten combining equations (9), (10) and (5) with (6), then the impedance modulus can be given by:

$$|Z| = \frac{L}{A} \sqrt{\left(\frac{1}{\sigma_h^2} \frac{1}{(1-k)^3}\right) + \left(\frac{1}{4\pi^2\varepsilon^2} \frac{1}{f^2}\right)}, \quad (11)$$

The impedance modulus can also be expressed as function of the volumetric conductive fraction, so that:

$$|Z| = \frac{L}{A} \sqrt{\left(\frac{1}{\sigma_h^2} \frac{1}{\phi^3}\right) + \left(\frac{1}{4\pi^2\varepsilon^2} \frac{1}{f^2}\right)}, \quad (12)$$

The analyzing expressions for volumetric conductive fraction take into account the composite material, the plasma and the red cells, so that:

$$V_s = V_c + V_i, \quad (13)$$

where V_s is the blood volume (composite material), V_c is the conductive material volume (plasma), and V_i is the volume of insulating material (red cells and glucose molecules). As already mentioned the volumetric fraction of the high conductivity phase is given by:

$$\phi = 1 - k, \quad (14)$$

where $\phi = \frac{V_c}{V_s}$ e $k = \frac{V_i}{V_s}$.

These definitions are in a fully agreement with EMT, since the constants reinterpretation occurs less than a linear transformation over the same parameters. However, the volumetric fractions ϕ and k are not fixed, as their values change with glucose concentration. This hypothesis is in contradiction to EMT, once the blood vessel volume should also be considered fixed in this first model approach.

If one considers the cylindrical volume occupied by the plasma, glucose molecules and red cells, then it is easy to note that red blood cells are much larger in volume and mass than glucose molecules and other ionic components present in blood. This implies that red cells have much larger inertia than plasma and glucose molecules. Therefore, it can be assumed that changes in glucose concentration only affect the volumetric fraction of plasma, which is here represented by ϕ . Then, it can be formulated from equation (14) that:

$$\phi - k' = 1 - k \quad (15)$$

where k' is the volumetric fraction of glucose, k is the volumetric fraction only assigned to red blood cells, while ϕ is still related to plasma.

Combining equations (15) and (12), the blood impedance modulus as a function of glucose concentration can be expressed by:

$$|Z| = \frac{L}{A} \sqrt{\left(\frac{1}{\sigma_h^2 (1 - k + k')^3} \right) + \left(\frac{1}{4\pi^2 \epsilon^2 f^2} \right)} \quad (16)$$

It is known that the electrical permittivity varies from one to another biological materials depending on the ions type and excitation frequency. This is also based on the polarization orientation caused by the application of a magnetic field to the material [28]. It is known that atoms, molecules and defect of materials re-adjust to an equilibrium in response to an applied electric field. This re-adjustment of atoms, molecules and defect of materials in response to an electric field is known as dielectric relaxation. The relaxation behaviour depends on the lattice properties, frequency, and temperature [29]. Materials that exhibit a single relaxation time constant can be modeled by the Debye's relation [28], which is given by:

$$\epsilon(\omega) = \epsilon_\infty + \frac{\Delta\epsilon}{(1 - j\omega\tau)} \quad (17)$$

where $\omega = \frac{1}{2\pi f}$, ϵ_∞ is the electrical permittivity at higher frequency, $\Delta\epsilon = \epsilon_s - \epsilon_\infty$, ϵ_s is the static permittivity at low frequency and τ is the environment's relaxation time characteristic.

As a result, the proposed impedance modulus as a function of glucose concentration can be formulated by combining equations (17) and (16), so that:

$$|Z| = \sqrt{\left(\frac{L^2}{A^2} \frac{1}{\sigma_h^2 \phi^3} \right) + \frac{(L - j2\pi\tau Lf)^2}{f^2 [2\pi A(\epsilon_\infty + \Delta\epsilon) - 4\pi^2 A\epsilon_\infty j\tau f]^2}} \quad (18)$$

3. Results

Figure 2(a) shows the impedance spectrum for different glucose concentrations. Equation (18) was normalized and rewritten in terms of $\sigma_m, \sigma_h, L, A, \epsilon_\infty, \Delta\epsilon, \tau$ and f . The new set of dimensionless constants are: $Z = Z/Z_{norm}$; $k = k/k_{norm}$, $k' = k'/k'_{norm}$; $f = f/f_{norm}$. The constants a, b, c, d and g in equation (19) represent a relative variation of Z in terms of blood volume, glucose concentration and frequency, respectively. The factor Z_{norm} is obtained by means of L and A, k'_{norm} by both glucose molar and volumetric densities, and f_{norm} by the blood's electrical permittivity.

The impedance spectrum is calculated by varying the dimensionless glucose concentration factor k' from 0.0040 to 0.0068, as shows Figure 2. The experimental data shows a noticeable relation with the model proposed by equation 18. Besides adimensionality, equation 18 can be fitted by experimental data.

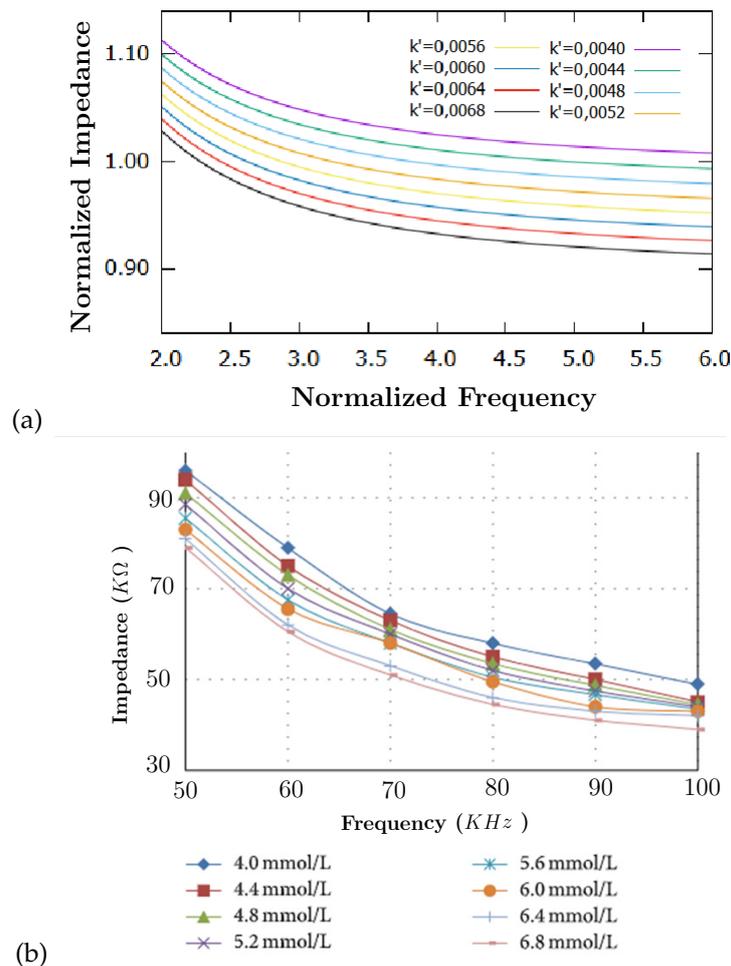


Figure 2. Normalized impedance spectra calculated by the proposed mathematical model (a) and the experimental data (b) presented by [5] (License CC BY 3.0 at <https://creativecommons.org/licenses/by/3.0>).

The equation (18) calculations were compared to the experimental data shown in [5] by using the least square method. The glucose concentration used in this comparison was 4.0 mmol/L. Equation (18) can be converted into a polynomial form as a function of frequency, such as:

$$|Z| = \sqrt{b + \frac{(a + cf)^2}{f^2(g + df)^2}}, \quad (19)$$

where $a = L, b = \frac{L}{A} \frac{1}{\sigma_h^2 (1-k+k')^3}, c = -2L\pi j\tau, d = -4\pi^2 A\epsilon_\infty j\tau$ and $g = 2\pi A(\epsilon_\infty + \Delta\epsilon)$.

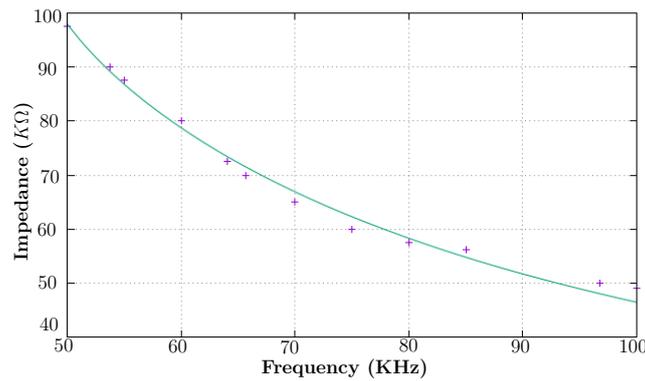


Figure 3. Frequency response of the modeled impedance data for a glucose concentration of 4.0 mmol/L.

Table 1 presents the errors associated in the fitting process, which are norm's maximum errors at the least squares method.

Table 1. Coefficient values from (19) and percentage errors.

Coefficient	Value	Error %
a	-1.12600×10^0	4.0
b	$+5.07358 \times 10^{-3}$	7.0
c	$+2.60469 \times 10^{-2}$	4.0
d	-5.64804×10^{-6}	4.0
g	$+2.45902 \times 10^{-4}$	4.0

Table 2 shows the deviations between modeled and experimental data, where the estimated constants in Table 1 were replaced in equation (19). Notwithstanding, the model presents a major error at 70 kHz frequency. This corresponds to the apparent anomaly in Figure 2(b), which might be a measurement error.

Table 2. Comparison between calculated impedance from equation (19) with the experimental one extracted from Figure 2(b) and the respective errors.

$f(\text{kHz})$	$Z_{\text{numeric}}(\text{k}\Omega)$	$Z_{\text{experimental}}(\text{k}\Omega)$	Error %
50.0	97.9	97.5	0.5
55.0	86.8	87.5	0.8
60.0	78.7	80.0	1.6
65.6	71.6	70.0	2.2
70.0	66.9	65.0	2.9
75.0	62.3	60.0	3.8
80.0	58.3	57.5	1.4
85.0	54.8	56.2	2.6
96.0	48.0	50.0	4.0
100.0	46.4	49.0	5.2

4. Discussions

It was shown in Figure 2 that the numerical curve has a significant similarity to the experimental one, implying that the proposed model can be used for modelling in vivo impedance data in a frequency range from 50 to 70 kHz. It was observed that the impedance module decrease exponentially with increasing frequency, whereas the error between data increases as increasing frequency. It can be noted in Figure 2(b) that the impedance modulus converges to approximately 45 kΩ (± 5 kΩ) at 100 kHz, whereas in Figure 2(a) there is no data overlap even at high frequency. The discrepancy at

high frequency observed in Figure 2(b) might be explained by the cell membrane capacitance which, in turns, is responsible for the transport of ions within the cell nucleus. Therefore, this imposes a limitation to the proposed numerical model at higher frequencies. Further investigations need to be done in order to find the optimal frequency range for this glucose measurement method.

It must be emphasized that the impedance variation due to glucose concentration is much smaller than the frequency excitation itself. Therefore, further investigations regarding the influences of other blood constituents (e.g. vitamins, lipids, lactate, amino acids, metabolic wastes and electrolytes) upon impedance spectra must be carefully done. However, regarding the low blood glucose sensitivity into respect to impedance, a similar result using occlusion spectroscopy was also found by [30]. In this study, the authors carried out *in vitro* experiments in a glucose range concentration from 0 and 100 mg/dL at different hematocrit concentrations. The glucose concentration used in the study [30] is much higher than the one we used for modeling, as it can be seen in Figure 2(b). The study [30] verified that the glucose variation is quite insensitive to the occlusion spectroscopy intensity, whereas is very significant to the percentages of hematocrit and the signal wavelength. As a resume, the results found here and by [30] may denote a standard behavior of the human circulatory system, even using different measuring techniques.

Results at Figure 2(b) showed that the impedance spectra for glucose concentrations of 6.4 and 6.8 mmol/dL are quite different in comparison to other curves. This might suggest either a measuring procedure error or parasitic interference of the instrumentation. This difference was confirmed by the proposed numerical model, then not allowing a proper prediction for this type of behavior.

It was found a maximum error of 7.0% when calculating the coefficients from equation (19), which might be explained by the methodology adopted here for extracting the data from a plot-manual and visual inspection. We believe that having access to more experimental data into a wider glucose concentration range, both standard deviation and fitting errors might be reduced. Regarding Table 2, the maximum impedance error of 5.2% at 100 kHz can be explained by the non-idealities of the instrumentation used to measured the published data, specially at higher frequencies. Furthermore, this error could also be caused by the visual data extraction technique used in this paper.

Finally, the proposed analytical model may improve the performance and increase the accuracy of commercial glucometer devices. The equations presented here provided a crude understanding of the physics behind the blood conductivity, which sheds light on the dynamic behavior between the blood glucose concentration and its electrical parameters.

5. Conclusion

Regarding the mathematical relationship between blood glucose concentration and its electrical impedance, BIA technique was presented as a suitable method when developing noninvasive glucose measurements into comparison to other noninvasive techniques. Moreover, the proposed mathematical modeling could confirm the validity of the hypothesis, where Bruggeman's effective medium equation can be satisfactorily used for modelling the blood conductivity as a function of its glucose concentration. Even the proposed model is simple, we could qualitatively explain the behavior of blood's impedance into respect to its glucose concentration upon a short frequency range.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

BIA	Bioimpedance analysis
ANN	Artificial neural networks
EMT	Effective Medium Theory

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