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Research Article

A Proposed Method for Detecting Blood Diseases by Non-Invasive Bio-Impedance Analysis

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Abstract: The main objective of this research is to represent a proposed method for detecting the blood diseases non-invasively by using the bio-impedance analysis. Blood with its components is good application of bioimpedance whereas each component has specific electrical properties. These electrical properties are changed with frequency. From this point, new model representing the blood components is proposed and described by mathematical equations. In this model the blood is divided into layers of different components such as RBCs, WBCs, plasma, etc. Each layer which represents one component has thickness related to its concentration within the blood and specific electrical properties. The proposed model of blood facilitates the expression of all blood components at different bands of frequencies. Finally, the paper presents procedures for blood analysis based on the proposed model of blood and the mathematical equations.

Keywords: Bio-impedance, mathematically, non-invasively, plasma, RBCs, WBCs

INTRODUCTION

Blood is the vital body fluid which consists of different cells suspended in plasma (around 55% of blood volume). The blood cells are RBCs, WBCs and Platelets. Red blood cells (around 44% of blood volume), while WBCs and platelets occupy around <1% (Starr and McMillan, 2016).

Any change in the concentrations of blood cells can cause many diseases such as anemia, polycythemia, leukocytosis, leukopenia, hemorrhaging, thrombosis, etc. (Damjanov, 2017; McCrae, 2006). Other diseases may cause deformations in the structure of blood cells such as diabetes mellitus, malaria and cancer. These diseases have toxic effects on the cells, leading to restructuring their membranes. As a result, some of the cells properties are changed such as the electrical properties (Starodubtseva *et al*., 2008; Desouky, 2009). In the case of plasma; abnormal concentrations of proteins change its electrical properties (Burtis *et al*., 2012).

Cholesterol is fat-like substance which found also in blood. For normality, the total cholesterol in blood (TC) is around 5 mmol/L which represents around 0.187% of blood volume (Aristovich, 2014). The increase in cholesterol level in blood, increase the probability of forming plaques (Barber *et al*., 2012). Hence the blood analysis is very important to detect various diseases.

The conventional method for blood analysis requires a blood sample taken from the patient by an invasive procedure. This method has many disadvantages such as infection transmission. Moreover, frequent blood sampling may cause bruise, bleeding and hematoma (Abdurrahman, 2003). The non-invasive techniques have been used in blood analysis to avoid the problems related to withdrawing the blood samples (Khalil *et al*., 2014; Malahov *et al*., 2010).

There are various non-invasive techniques used for blood analysis such as optical spectroscopy, photo acoustic spectroscopy, thermal emission spectroscopy and ultrasound technology. The limitation of these techniques are being sensitive to motion artifacts, interfaces, skin temperature, low signal to noise ratio and therefore need extensive data processing (Amaral, 2008).

Bio-Impedance Analysis (BIA) is recently used for detecting body diseases. This analysis (BIA) is non-invasive and relatively simple in measurement. In BIA, electrodes are used to apply an alternating current and measure the resultant potential. The impedance is calculated as the ratio of the resultant voltage to the applied current at the corresponding electrodes. When the current passes through the human body, two components are observed named resistance and capacitance. The resistance is related to the intracellular and extracellular fluid, while the capacitance is related to the cell membrane (Alrawi *et al*., 2010).

As mentioned before, the blood consists of plasma and different cells. The plasma is good conductor to the current because it is mostly water. Conversely are the

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cholesterol molecules that are poor conductors. The behavior of blood cells is different because each cell is surrounded by membrane. At very low frequencies, this membrane is electrically as insulator. As the frequency is increased, more current can pass through the cell. At higher frequencies; the cell membrane is considered as short circuit and no longer impedes the current flow. Consequently, the current can take a direct path through the cell and thus cells aggregation and orientation has no effect on the impedance (Gaw, 2010). At very high frequencies, the electrical properties of cells are close to those of the medium (plasma) (Kadir *et al*., 2012).

The presentation of blood with its components is important. The blood Cells and cholesterol particles can be presented as (spheres and cylinders) in a conductive liquid (plasma) such as the model proposed by Aristovich (2014). This model is the closest to reality in describing the blood components. But the problem is in the difficulty of being constructed using the software programs and in mathematical description. In this study simplified model of blood is presented under the application of AC-current with different bands of frequencies. The blood is modeled as layers of (plasma, RBCs, WBCs, platelets and cholesterol). All layers have the same cross section area. Hence, each component (layer) has specific electrical properties and a thickness related to its volume percentage in blood.

This study is arranged as the following:

- Finite element model of the Whole blood is constructed. The electrical properties of blood with different cases are collected from measured database.
- The proposed model of blood is also constructed. The blood components are represented as layers with specific thicknesses and electrical properties.
- The study presents mathematical algorithm which describe the blood components at different bands of frequencies.
- Finally, the paper proposes new method for analysis the blood components non-invasively using the proposed model of blood and its mathematical algorithm. The analysis includes estimating the volume and electrical properties for each blood component and therefore, the blood diseases can be detected.

MATERIALS AND METHODS

The blood model was performed at the end of 2017 by the software program (COMSOL Multiphysics 5.0), using a machine with Intel Core i5 and 64-bit operating system

COMSOL Multiphysics 5.0 is preferred for simulating the blood inside a body part to apply a non-invasive study. The selected part is the earlobe, because it does not contain bone inside it and filled with capillaries. The average blood volume in the earlobe is around 14% (Waugh and Grant, 2014). Aristovich (2014) has used the earlobe before to detect the cholesterol level in blood but this blood volume has not been taken into account.

The 3D models are constructed by COMSOL in three stages (Fig. 1).

First stage: The first stage includes the choice of space dimension, physics and study. The 3D space is chosen to model the blood inside earlobe. Then "electric current" physics and frequency domain study are selected to apply ac current with different frequencies.

Second stage: The second stage includes five steps: building the model geometry, selecting the materials, adjusting the physics, determining mesh setting and finally adjusting the study.

In the first step, two models (model.1 and model.2) are built with the same procedures.

Model.1: Figure 2 and 3, 3D model of the blood inside a simplified human earlobe is constructed. The earlobe is modeled as a structure consisting of three domains: skin, soft tissue (adipose tissue) and blood. The total earlobe thickness is assumed to be 5 mm. It is divided into: 1 mm upper skin, 1 mm lower skin, 0.7 mm blood which represented 14% of the total earlobe thickness and the remainder is soft tissue. The average earlobe diameter is 2 cm and all domains have the same area.

Also, simple configuration of electrodes is used in this model. Two electrodes are used in supplying the ac-current and in voltage measurements. The two electrodes are located at the different sides of earlobe.

Model.2 (Proposed model): Two electrodes at different sides of the earlobe enable the current to pass through all layers of earlobe and thus through all blood volume. This blood volume consists of around 45% RBCs, 1%WBCs and Platelets, 0.187% cholesterol and the remainder is plasma (Starr and McMillan, 2016; Barber *et al*., 2012).

Figure 4 and 5 indicate to the proposed model of blood. This model describes all blood components and the passage of current through them. The blood is divided into (RBCs, WBCs, Platelets, cholesterol and plasma). Each component is represented as layer. The thickness of each layer represents the volume percentage of this component in blood. Furthermore; each layer has specific electrical properties. This model is used to facilitate the study of blood components separately by representing them as layers.

Figure 4 and 5, the 0.7 mm blood thickness is divided into: -0.315 mm RBCS, 0.0035 mm WBCS, 0.0035 mm platelets, 0.001309 mm cholesterol and the remainder is plasma. All layers have the same cross sectional area; also the arrangement of these layers in the model has no effect on the measured impedance.

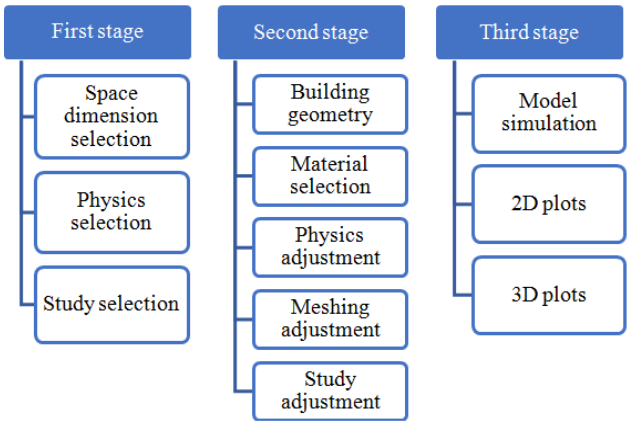


Fig. 1: 3D Model 1 by COMSOL

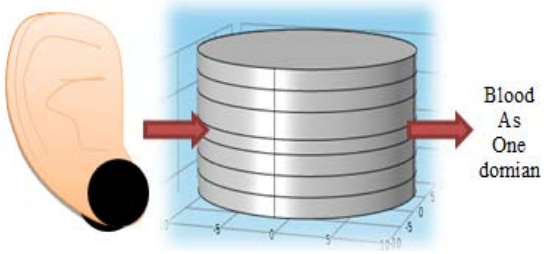


Fig. 2: Model 1, the geometry of earlobe and blood inside it

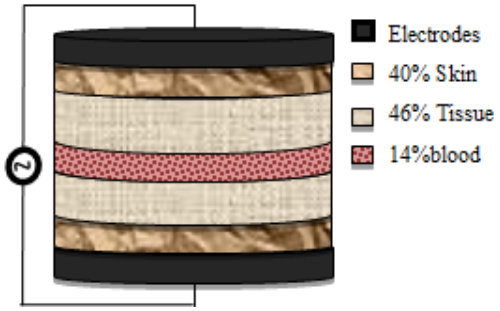


Fig. 3: Illustrated figure of Model 1

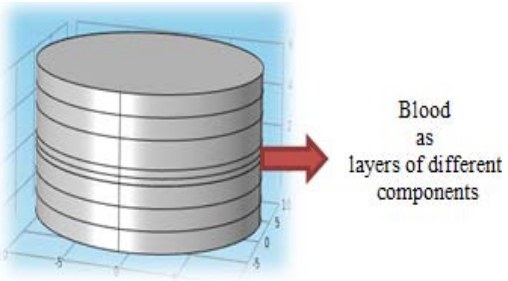


Fig. 4: Model.2, blood is represented as layers of its components

In the second step, the materials are selected.

The copper is used copper for electrodes. Frequency dependent dielectric properties for the blood,

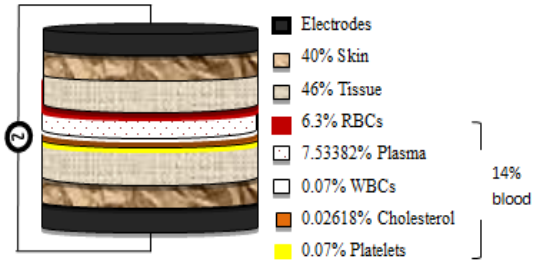


Fig. 5: Illustrated figure of Model.2

wet skin, adipose tissue and cholesterol (fat) have been defined using the database developed by Gabriel *et al*. (1996). The electrical properties of blood components at different frequencies are collected for RBCS (Kotb *et al*., 2014; Beving *et al*., 1994), WBCS (Polevaya *et al*., 1999; Yang *et al*., 1999), platelets (Piacentini *et al*., 2011) and plasma (Wolfa *et al*., 2011).

In the third step, the used physics is adjusted.

In the electric current physics, the upper electrode is chosen to be terminal with current value 1mA and the lower electrode is the ground.

The fourth step is selecting the mesh setting. The extra-fine element size is selected in meshing for each model to increase the model efficiency as shown in Fig. 6.

Finally, in frequency domain study, the used frequencies are from 1 KHZ to 10 GHZ.

The third stage: In this final stage, the simulation is performed in each model and the impedance values are measured across the electrodes within 1 kHz to 10 GHz. The models results are extracted and compared together.

MATHEMATICAL ALGORITHM

This part introduces the proposed mathematical model of blood. This proposed model is based on

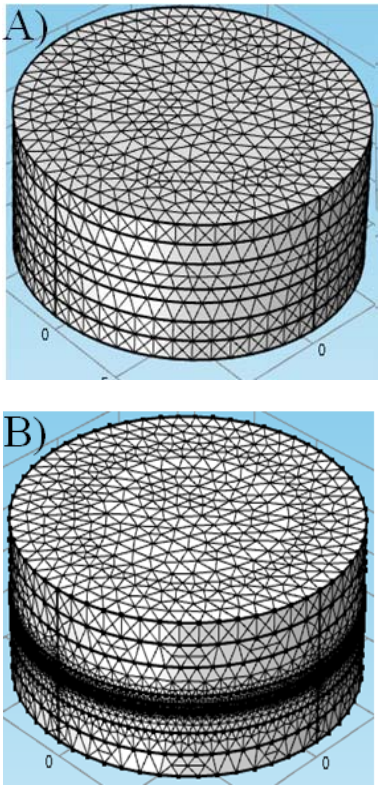


Fig. 6: Mesh with extra-fine element size. A) Model.1.B) Model.2

specific equations which present the blood as layers of plasma, RBCs, WBCs, platelets and cholesterol with the same area. The equations are stated in different bands of frequencies. The impedance general law is:

$$Z = \frac{d}{A*(\sigma+jw\epsilon)} \quad (1)$$

where,

A : The area
d : Thickness
σ : The electrical conductivity
$\epsilon = \epsilon_0\epsilon_r$: The permittivity
ϵ_0 : The Vacuum permittivity
ϵ_r : The relative permittivity

The electrical conductivity and permittivity are function of frequency (Chetty and Yang, 2011).

The blood impedance is represented by the following equation:

$$Z_{blood}=\frac{d_b}{A*(\sigma_b+jw\epsilon_b)} \quad (2)$$

where, d_b, σ_b and ϵ_b are the thickness, the electrical conductivity and the permittivity of the blood. A is the area. Thus, the impedance of whole earlobe (Model.1, in Fig. 2):

$$Z_{earlobe1}=\frac{d_b}{A*(\sigma_b+jw\epsilon_b)}+\frac{ds}{A*(\sigma s+jw\epsilon s)}+\frac{da}{A*(\sigma a+jw\epsilon a)} \quad (3)$$

where,

ds and da = The total thicknesses of skin and adipose tissue layers
σ_s and σa = The electrical conductivity of skin and adipose tissue
ϵ_s and ϵa = The electrical permittivity of skin and adipose tissue

Equation (2) deals with the whole blood as one domain and gives no information about its components. Thus modification in Eq. (2) is applied to represent the blood components separately:

$$Z_{bloodlayers}=\frac{d_R}{A*(\sigma_R+jw\epsilon_R)}+\frac{d_w}{A*(\sigma_w+jw\epsilon_w)}+\frac{d_p}{A*(\sigma_p+jw\epsilon_p)}+\frac{d_c}{A*(\sigma_c+jw\epsilon_c)}+\frac{d_{pl}}{A*(\sigma_{pl}+jw\epsilon_{pl})} \quad (4)$$

d_R, d_w,d_p, d_c and dpl are the thicknesses of RBCs, WBCs, platelets, cholesterols and plasma layers.

σ_R, σ_w, σ_p, σ_c and σ_{pl} are the electrical conductivity of RBCs, WBCs, platelets, cholesterols and plasma.

ϵ_R, ϵ_w, ϵ_p, ϵ_c and ϵ_{Pl} are the electrical permittivity of RBCs, WBCs, platelets, cholesterols and plasma. The impedance of whole earlobe (Model.2, in Fig. 4):

$$Z_{Earlobe2}=\frac{d_R}{A*(\sigma_R+jw\epsilon_R)}+\frac{d_w}{A*(\sigma_w+jw\epsilon_w)}+\frac{d_p}{A*(\sigma_p+jw\epsilon_p)}+\frac{d_c}{A*(\sigma_c+jw\epsilon_c)}+\frac{d_{pl}}{A*(\sigma_{pl}+jw\epsilon_{pl})}+\frac{ds}{A*(\sigma s+jw\epsilon s)}+\frac{da}{A*(\sigma a+jw\epsilon a)} \quad (5)$$

In the frequencies up to 100 kHz, the imaginary part ($jw\epsilon$) of blood and blood components has small value and can be ignored (Visser *et al*., 1988). And thus Eq. (3) and Eq. (5) are simplified into:

$$Z_1=\frac{d_b}{A*(\sigma_b)}+\frac{ds}{A*(\sigma s+jw\epsilon s)}+\frac{da}{A*(\sigma a+jw\epsilon a)} \quad (6)$$

$$Z_2=\frac{d_R}{A*(\sigma_R)}+\frac{d_w}{A*(\sigma_w)}+\frac{d_p}{A*(\sigma_p)}+\frac{d_c}{A*(\sigma_c)}+\frac{d_{pl}}{A*(\sigma_{pl})}+\frac{ds}{A*(\sigma s+jw\epsilon s)}+\frac{da}{A*(\sigma a+jw\epsilon a)} \quad (7)$$

Z_1 and Z_2 are the earlobe impedances in the frequencies up to 100 kHz.

At high frequency (At the end of MHZ and in GHZ), the electrical properties of cells are close to plasma. Thus, the blood cells (RBCs, WBCs and platelets) and plasma are appeared approximately as one component. In this study, RBCs, WBCs, platelets and plasma are assumed to be one layer. This layer has the same electrical properties of plasma. The layer is named as 'conducting fluid' and its thickness equals to the total thicknesses of RBCs, WBCs, platelets and plasma as shown in Fig. 7. Eq. (5) becomes:

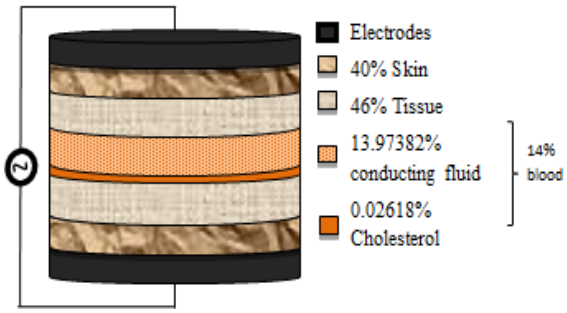


Fig. 7: Illustrated figure of blood layers inside a simplified earlobe in GHZ range

$$Z_{GHZ}=\frac{d_c}{A*(\sigma_c+jw\epsilon_c)}+\frac{d_{cf}}{A*(\sigma_{cf}+jw\epsilon_{cf})}+\frac{d_s}{A*(\sigma_s+jw\epsilon_s)}+\frac{d_a}{A*(\sigma_a+jw\epsilon_a)} \quad (8)$$

Z_{GHz} is the earlobe impedance at frequency in GHZ range. d_{cf}, σ_{cf} and ϵ_{cf} are the thickness, electrical conductivity and electrical permitivity of conducting fluid l.

In this case, the blood is represented as non-conducting spheres (cholesterols particles) suspended in conductive medium (plasma and cells). Using hanai mixture equations, the electrical properties of blood with different volume fraction of cholesterol particles can be calculated (Hanai, 1960).

In the next section, comparisons are applied between the results of COMSOL models at wide frequency range:

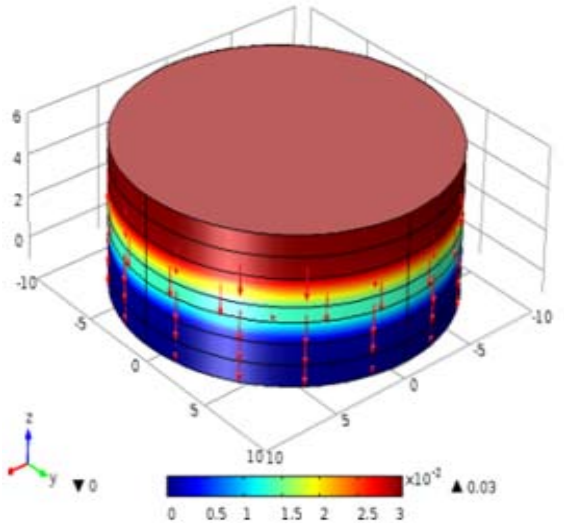
- Model.1, which dealing with blood as a whole with its electrical properties.
- Model.2, which representing the blood components as layers, each layer has specific thickness and electrical properties.

For investigating the validity of presenting the blood components as layers and determining the frequencies range that produced converged results.

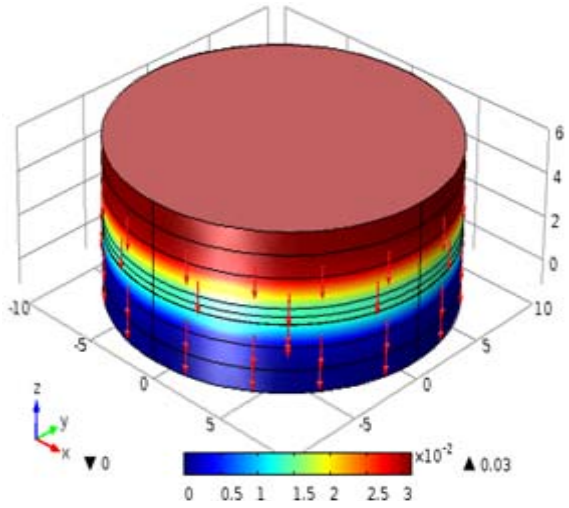
RESULTS

In this part, the detailed results are presented in two major categories as follows: First category, the distribution of electric field in model.1 and model.2. Second category, comparisons between the two models in different blood states which are the normal and diseased.

In the first category, the applied electric field is represented and described in model.1 as shown in Fig. 8A. Figure 8A shows the distribution of electric potential over the whole earlobe layers. The red arrows represent the current density from the first electrode to the second electrode. Thus, the current passes through all blood volume. This blood volume is divided into



(a)



(b)

Fig. 8: The distribution of electric field. (A) Model.1. (B) Model.2

five different volumes of (RBCs, WBCs, Platelets, cholesterol and plasma) as shown in Fig. 8B.

In the second category, the impedances of the two models are compared together.

The study of blood properties in normal case: Figure 9 and 10 show the impedance values of whole earlobe measured from the models: model.1 and model.2 at different frequencies.

Figure 11 to14 shows the resistance and reactance values of model.1 and model.2.

Figures from (9-14) show small differences between the impedance values in the frequencies <100 KHZ. These differences are disappeared by increasing the frequency. This means that, the proposed model of

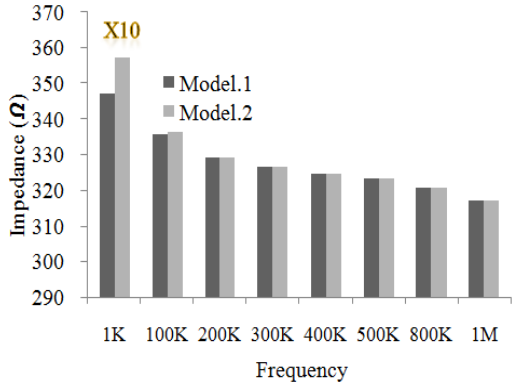


Fig. 9: The impedance values of the two models from (1 KHz to 1MHz)

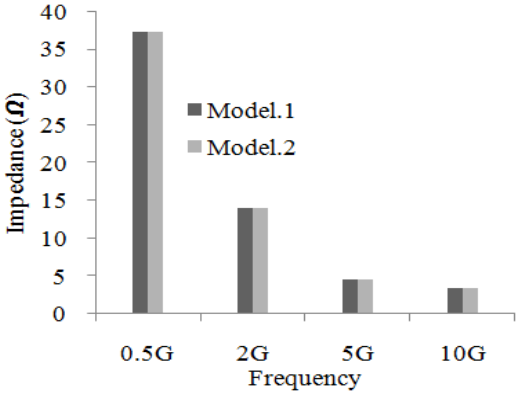


Fig. 10: The impedance values of the two models from (0.5GHz to 10GHz)

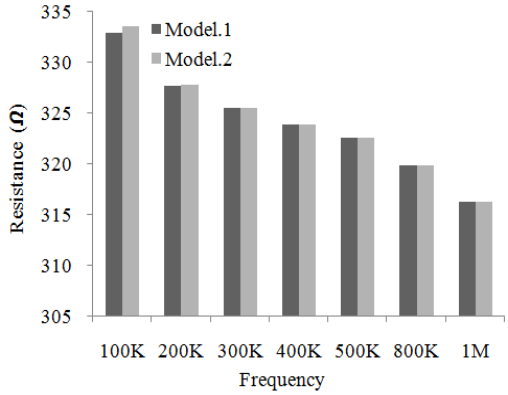


Fig. 11: The resistance values of the two models from (100 KHz to 1MHz)

blood (model.2) is valid to represent the blood components at frequencies >100KHZ.

The study of blood properties in different pathological cases: The proposed model of blood components is also tested in two pathological cases.

- Blood with different HCT%
- Blood with different cholesterol concentration.

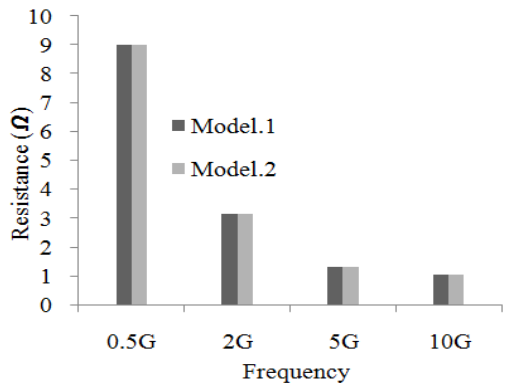


Fig. 12: The resistance values of the two models from (0.5GHz to 10GHz)

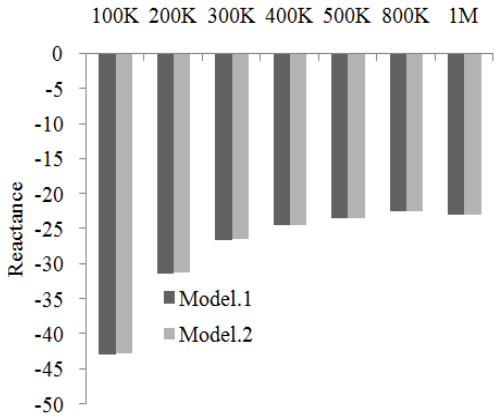


Fig. 13: The reactance values of the two models from (100 KHz to 1MHz)

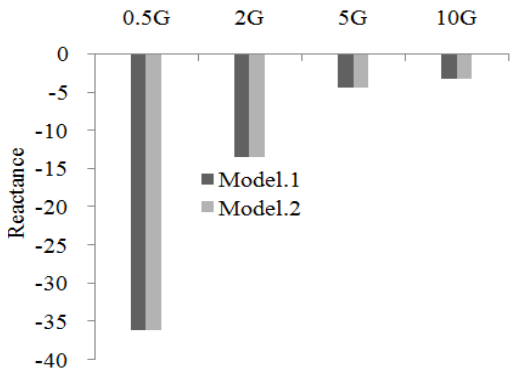


Fig. 14: The reactance values of the two models from (0.5GHz to 10GHz)

Modifications are applied on the models (model.1, model.2) to represent various blood diseases.

Blood diseases are represented:

- In model.1, as a change in the electrical properties of whole blood.
- In model.2 as a change in the layers thicknesses

Table 1: Relative permittivity of whole blood at different frequencies (Wolfa *et al*., 2011)

Frequency	100 KHz	200 KHz	300 KHz	400 KHz	500 KHZ	1000 KHZ
Blood relative permittivity	5120	4925	4695	4445	4188	3026

Table 2: Different thicknesses of RBCs layer corresponding to the HCT%

HCT	25%	30%	35%	40%	45%	50%	55%
RBCs layer (mm)	0.175	0.21	0.245	0.28	0.315	0.35	0.385

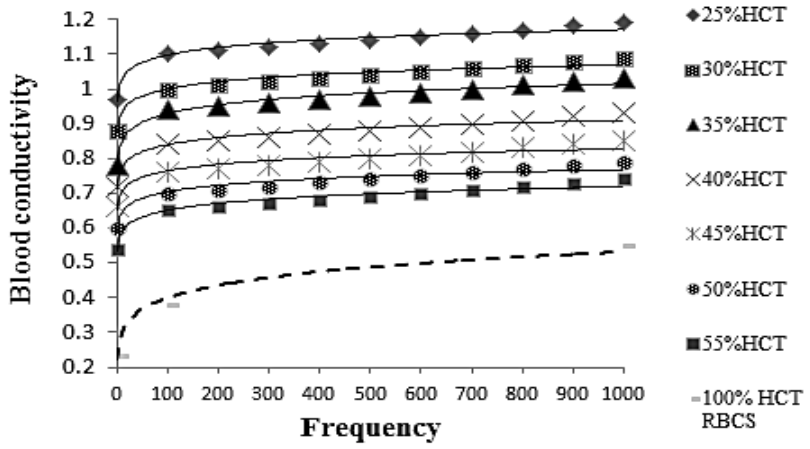


Fig. 15: Electrical conductivity of whole blood at different frequencies (Wolfa *et al*., 2011)

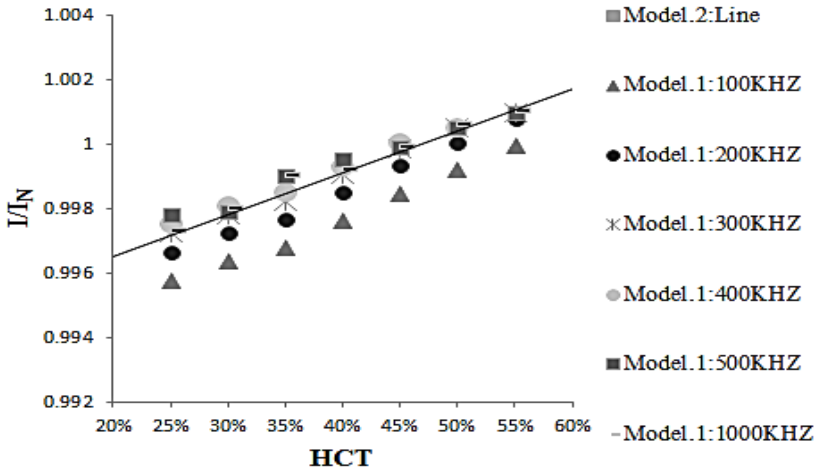


Fig. 16: I/I_N values at different HCT

The blood properties with different HCT: In model.1, the impedance values are measured using the electrical properties of whole blood at different HCT in Fig. 15 and Table 1. In model.2, the impedance values are measured using different thicknesses of RBCs layer corresponding to the HCT% as shown in Table 2. The thickness of the plasma layer is reduced by the same amount as the increase in RBCs layer. The other parameters are not changed.

Figure 16 shows Comparisons between the impedance values measured from the two modified models at different HCT, using different frequencies. Where 'I' is the measured impedance at different HCT and 'I_N' is the measured impedance at 45% HCT. The solid line represents the regression line for model.2 results at different frequencies. While the data points represent the model.1 results.

Figure 16 displays differences between the two modified models in frequencies <100KHZ. In the frequencies >100KHZ, these differences disappear.

The influences of changing the concentrations of blood cells (%) and cholesterol on the measured impedance are studied in GHZ range.

Figure 17 illustrates that, in the frequency around 2GHZ, the increment in cells volume from (30% to 60%) has an ignored effect on the measured impedance as the electrical properties of cells are near to plasma. Conversely, any change in cholesterol concentration changes the measured impedance.

Table 3: Electrical properties of whole blood at different at different frequencies (Hanai, 1960)

	2GHZ		5GHZ		10GHZ	
Cholesterol volume %	σ	ϵ	σ	ϵ	σ	ϵ
Conducting fluid (0 %)	2.2	59.16	8.32	50.5	13.2	45.2
0.187%	2.185	58.99	8.296	50.39	13.131	45.1
0.33%	2.181	58.87	8.278	50.2	13.1	44.9
0.47%	2.176	58.74	8.26	50.1	13.07	44.8
0.615%	2.171	58.6	8.24	50	13.04	44.7

Table 4: Different thicknesses of Cholesterol layer

Cholesterol volume %	0.187%	0.33%	0.47%	0.615%
Cholesterol layer	0.001309	0.00231	0.00329	0.004305

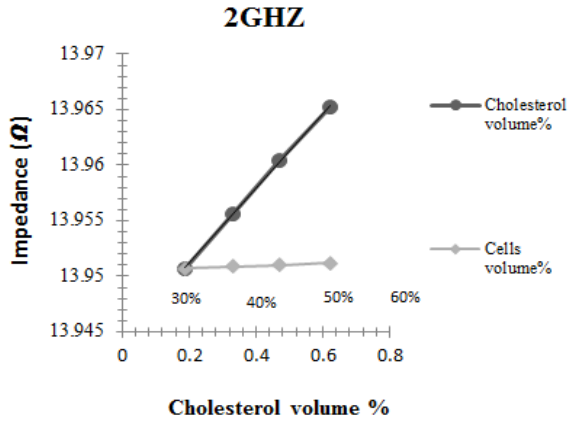


Fig. 17: Impedance values at different volumes of cells cholesterol at 2GHZ

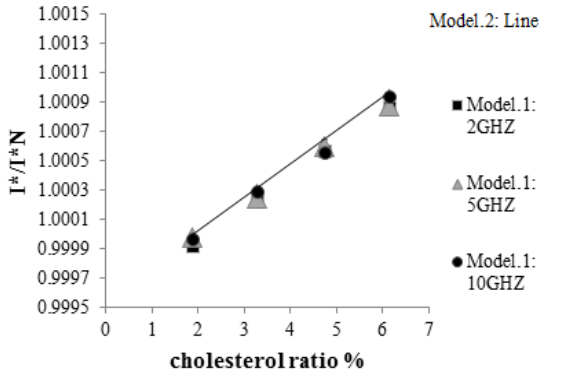


Fig. 18: I*/I*N values at different volume percentage of cholesterol in blood

The blood properties with different concentrations of blood cholesterol: The frequency of the applied current is in GHZ range. In model.1, the impedance values are measured using the electrical properties of whole blood with different volume percentage of cholesterol calculated by hanai mixture equations in Table 3. In model.2, the impedance values are measured at different thicknesses of cholesterol layer corresponding to the cholesterol concentration in blood as shown in Table 4.

Figure 18 shows Comparison between the impedance values of the two modified models at different cholesterol concentrations. Where 'I*' is the measured impedance at different volume percentage of cholesterol and 'I^*_N' is the measured impedance at 0.187% cholesterol. The solid line represents the regression line for the model.2 results at different frequencies. While the data points represent the impedance values of model.1.

Figure 18 shows that the results of two models are close especially in the frequencies>2GHZ.

DISCUSSION

From the models results, the results show the validity of model.2 and thus its described equation for representing the blood components and their diseases in the frequencies >100 KHZ. It is clear from Fig. 9 to 14, Fig. 16 and 18 that the differences between the models results are disappeared in the frequencies between [100KHZ and 10GHZ].Whereas, at low frequencies, the distribution of blood cells, their orientations and aggregations influence on the measured impedance and vice versa at high frequencies (Gaw, 2010; Wolfa *et al*., 2011). Also the random distribution of cells in plasma affects the current path between the two electrodes and thus affects the blood impedance. These factors make the representation of blood components is difficult and thus the proposed model of blood and its described equations are not valid for usage in these low frequencies.

The paper offers significant advantages over many other researches e.g., Aristovich (2014) in modeling the blood components. The presentation of blood cells as (spheres and cylinders) in plasma is complex to be constructed. Subsequently, errors cannot be ignored, are produced due to 3D problems and cells overlapping. Also the representation of cells and particles in this way is very complex to be expressed mathematically

The main objective of this study is to introduce a simple blood model under the application of ac current. The blood components are introduced by their volumes as layers with different thicknesses and electrical properties. This simplified model facilitates the expression of all blood components mathematically and thus can be used in estimating the properties of each component.

Final part: Proposed method for analysis the blood components: Finally, the proposed procedures wished to be used for blood analysis are presented using the

stated mathematical algorithm and the measured impedances of earlobe as shown in Fig. 19.

The thicknesses and electrical properties of different blood components (layers) would be estimated. This is done by reverse process using the measured impedances of earlobe at different frequencies and the stated Eq. (4-8). Also calculations would be applied to find the thicknesses of earlobe

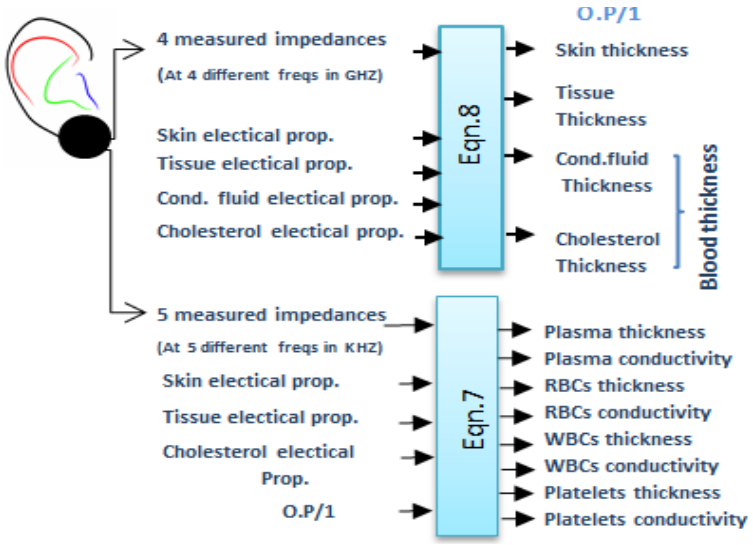


Fig. 19: The inputs and outputs for blood analysis

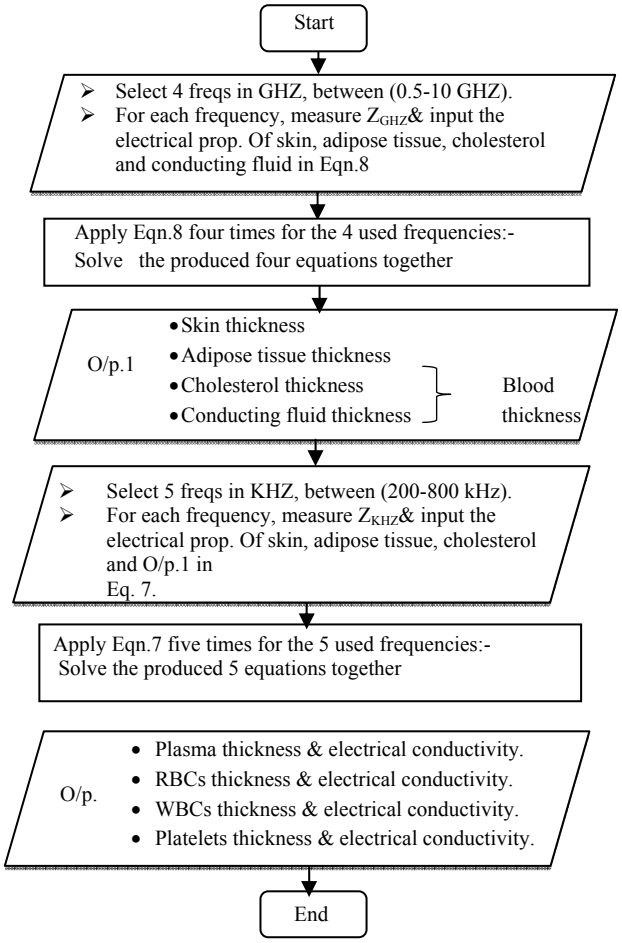


Fig. 20: Flows chart for analysis the blood components and the earlobe tissues

layers (skin, tissue and blood), as they differ from person to other. The electrical properties of skin, adipose tissue, conducting fluid and cholesterol at each frequency are knowns. They are assumed not to be changed with blood diseases. Also the imaginary term "jwϵ" is neglected in the frequencies between (200-800KHZ) as mentioned before.

The flow chart for analysis the blood components and the earlobe tissues is shown in Fig. 20.

After calculating the thickness of each layer (component), its volume percentage in blood is calculated as the ratio of component thickness to blood thickness. Consequently, the diseases related to the change in concentrations of blood components can be detected. Any change in the electrical properties of blood cells, indicates to deformations in these cells, while any change in the electrical properties of plasma indicates to abnormal concentrations of proteins.

The advantage of using non-invasive method in blood analysis is to overcome the problems related to withdrawing the blood sample by invasive method such as infection transmission, inflammation, bleeding, etc. Besides that, people with infectious diseases have special procedures in withdrawing the blood sample.

This research is conducted to study the possibility of using bioimpedance technique for checking and detecting the blood diseases .Generally; this method has many advantages over the other non-invasive methods such as: fast results, low-cost, simple measurements and ease of use.

The earlobe is selected as a place of electrodes to conduct the non-invasive analysis. If other parts such as arm, leg or finger are used in analysis, the prediction of current path and the portion of current that will reach the electrode become difficult. Also it increases the complexity of mathematical model to represent system contains skin, muscle, fat, blood and bone.

This study also suggests using a simple configuration of electrodes. Two electrodes are used in applying the current and measuring the voltage to avoid some effects such as interference, complexity of field distribution and parasitic capacitances. Some researches such as Pockevicius *et al*. (2013) use the inter-digital electrode, but this electrode is not used in this research due to its complexity.

CONCLUSION

This study presents new proposed model of blood components when applying alternating current with different frequencies. This is done by simplifying the blood and representing it as layers of different components. This simplified model facilitates the expression of the impedance of blood components mathematically. Taking into consideration that this proposed model can be used at specific frequencies as shown in the results. Also proposed procedures are presented finally to estimate the concentration and electrical properties of each component.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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