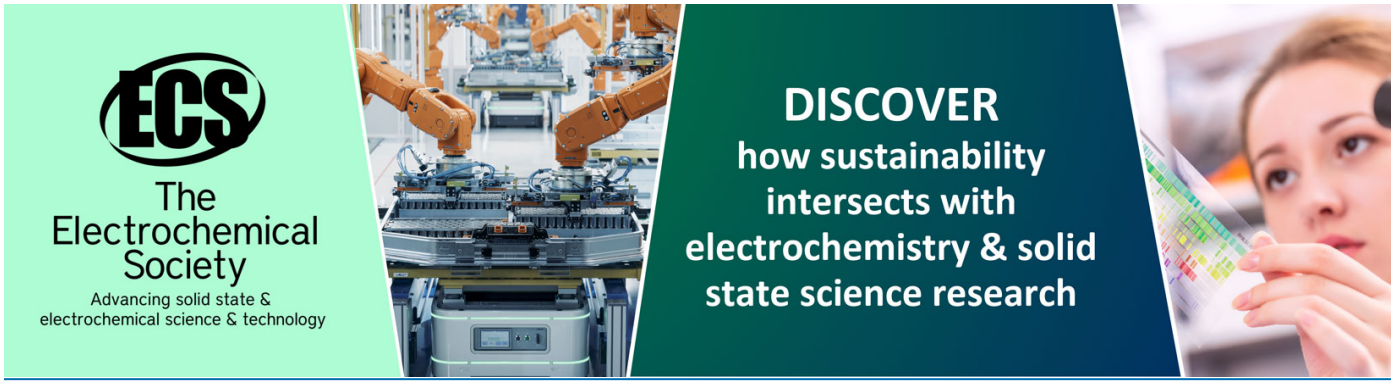
Non-invasive measurement of cholesterol in human blood by impedance technique: an investigation by 2D finite element field modelling



Non-invasive measurement of cholesterol in human blood by impedance technique: an investigation by 2D finite element field modelling

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Abstract. This paper concerns detection of solid particles suspended in conductive media by impedance technique. The technique is based on changes in impedance measured between two electrodes placed across a given volume of conducting medium. It presents a methodology for modelling and investigation of the feasibility of such a technique for particle detection by 2D finite element (FE) field modelling. This is based on modelling and computation of electric field distribution between the above electrodes. It establishes the modelling approach, the complexity involved and justifies the need for modelling in 3D to incorporate some of the effects that cannot be taken into account in 2D models. It reports on the modelling investigation for a specific case of detecting, by impedance technique cholesterol particles suspended in human blood and points to a possible instrument for non-invasive measurement of blood cholesterol level.

1. Introduction

Driven by concerns over public health associated with cardiovascular and other related diseases an easy, non-invasive, reliable and effective method for measuring cholesterol level in human blood is of increasing importance. There are at present a large number of direct and indirect methods that are available in clinical and research laboratories for the quantitative measurement of cholesterol in blood [1-3]. These measurements are being done increasingly frequently and often for prophylaxis and awareness against cardiovascular diseases. All these methods require a sample of the blood obtained from the body by an invasive procedure. The procedure may carry a risk of bruise, infection and/or hematoma. There are, however some indirect methods by which the level of total cholesterol can be estimated using bioelectrical impedance measurements carried out elsewhere in the body [4]. As these methods are indirect and based on inference of cholesterol level from statistical data obtained by multiple impedance measurements of substances other than blood, they are complicated, time consuming and often lack accuracy and reproducibility.

Thus, there is a growing need to develop a simple, non-invasive method for measuring total blood cholesterol. It is proposed to do this by using electrical impedance technique in which the conductivity distribution of objects (e.g. cholesterol particles carried by lipoproteins) within a volume (e.g. blood plasma) is measured in the form of impedance (Z) between a pair of electrodes. The impedance technique has been widely used in many areas (industry, chemical production, pharmacy, medicine, biosciences) and it has been proven to be reliable for imaging (EIT, ERT) [5-7] and quantitative analyses (BMI, fuel purity, impedance spectroscopy) [8-11].

The impedance technique has been used successfully for many biological measurements of human body, especially for measuring characteristics of blood. These include measurement of body fluid volume [12], fat [13, 14], glucose [15], blood coagulation [16], hematocrit (erythrocyte volume fraction, EVF) [17], white blood cell count and other blood measurements [18]. However the blood measurement methods used involve an invasive procedure for obtaining blood from the body.

As mentioned earlier, the proposed impedance technique for cholesterol measurement is non-invasive and, in this paper the feasibility of this technique has been established by 2D finite element modelling. This essentially comprises modelling of particles suspended in conductive media.

2. 2D mathematical modelling of particles suspended in conductive medium and its finite element realisation

2.1. Mathematical model and impedance calculation

Although the mathematical physics of conduction is well understood, the mathematics of describing the current and potential fields between and around impedance electrodes, particularly those attached to organic tissue, is more challenging.

For given potentials φ assigned to driving electrodes the electric field distribution in the 2D problem domain Ω (x, y) between the electrodes is given by the following Laplace's equation [19]:

$$\nabla^2\varphi = 0 \text{ in } \Omega \tag{1}$$

Under appropriate boundary conditions the above equation is solved by finite element method (FEM) [20] in terms of unknown electric potential φ for given conductivity (σ) and permittivity (ε) distributions in the problem Ω. It is assumed that the material properties are linear, piece-wise homogeneous and isotropic. Following the solution of equation (1), field intensity and flux density vectors $\mathbf{E}=-\text{grad}V$ (V is the potential difference between the driving electrodes) and $\mathbf{D}=\varepsilon\mathbf{E}$ can be calculated. From these the current $I=\mathbf{J}A$ (A is the cross-sectional area) is calculated using current density $\mathbf{J}=\sigma\mathbf{E}$. Finally, the impedance Z is calculated from the simple relationship between current (I) and voltage (V) between the electrodes:

$$Z = \frac{V}{I} \tag{2}$$

For the modelling studies reported in this paper the above field equation was solved using the commercial software package COMSOL [21].

2.2. Assumptions

The modelling and computation of electric field distribution in the problem domain is based on a number of assumptions some of which are either justified by modelling experiments or discarded by introducing further complexities in the subsequent FE models.

The main assumption taken in the studies reported here is that the electric field distribution between the driving electrodes mentioned above is two-dimensional and, it has been shown by modelling experiments that this is appropriate as a first approximation.

The human blood is a complex medium, which is composed of cells of different sizes and shapes (red blood cells, white blood cells, platelets, etc.) distributed in a conductive aqueous solution (blood plasma). About 55% of the blood fluid is composed of blood plasma (mostly water – 91.5%) and the remaining 45% consists of various blood components (various blood cells and other inclusions) [22]. This means from the electric field and conductivity points of view blood is essentially a non-homogenous and anisotropic medium. Specifically, this also means that the electrical properties of the whole blood (e.g. electrical conductivity, σ and the dielectric permittivity, ε) are different from those of blood plasma, which contains no cells [23, 24].

For all modelling purposes it was assumed that blood was linear, piecewise homogeneous and isotropic. The piecewise homogeneity can account for non-homogeneous properties of blood and its isotropy is justified by the fact that in the 2D problem domain the main components of electric field

(**E**, **D**) and current density vectors (**J**) are mainly confined in the *x*-*y* plane. Furthermore, it should be noted that for frequencies lower than 100 kHz most living tissues are assumed to be electrolytic conductors. At higher frequencies the dielectric properties of bio-tissue may dominate. The higher the frequency the closer the tissue properties come to those of water.

There are no eddy current effects for the range of frequencies (50 Hz to 100 MHz) which is normally used for measuring impedance of living tissues. At higher frequencies electromagnetic properties of tissue become very close to the properties of water, so no useful information can be obtained. The lowest skin depth in this context is 30 mm (for blood plasma at 100 MHz), which is significantly higher than the characteristic size of features and problem domain involved. Hence there are no eddy-current effects.

2.3. Finite element models

Figure 1 shows the basic 2D FE model of the problem domain Ω (*x*, *y*) in which Equation (1) was solved under the boundary conditions shown in Figure 2. The active problem domain in between the driving electrodes is surrounded by air regions ($\sigma = \sigma_1$) to account for any fringe and leakage fields. The blood-plasma region ($\sigma = \sigma_2$) in between the electrodes is also extended in the *y*-direction to account for fringe field effects, which need to be quantified. As shown in Figure 1 the cholesterol particles ($\sigma = \sigma_3$) are confined in the blood plasma between the electrodes.

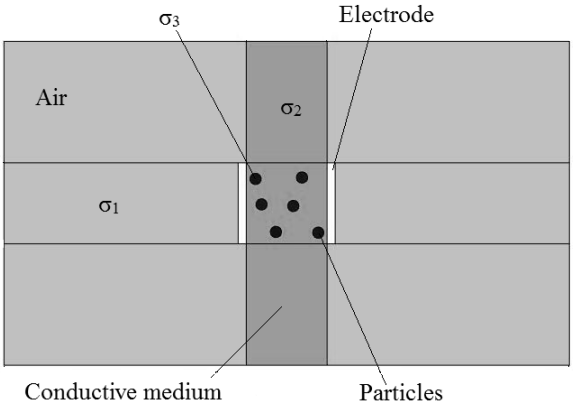

Figure 1. Basic 2D finite element (FE) model of particles in a conductive medium.

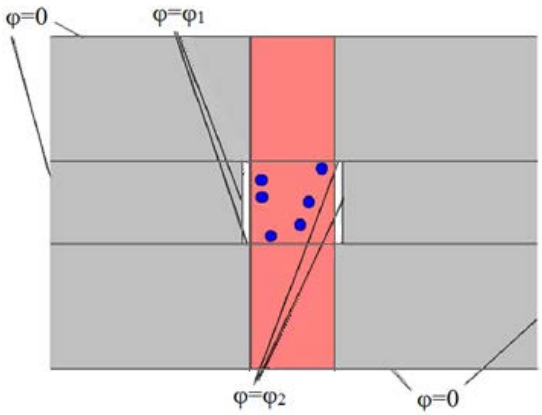

Figure 2. 2D finite element model showing boundary conditions.

The above FE models were used to investigate the effects of various parameters on the distribution of alternating currents and electric potential (hence voltage drops) in the problem domain. The parameters included various physiological (e.g. level and distribution of lipoproteins/cholesterol, other

blood components), material (e.g. dielectric permittivities (ε) and conductivities (σ) of blood components including lipoproteins carrying cholesterol particles). This can also be used to investigate the effects of electrical variables (e.g. measurement circuitry, excitation frequency, electrode geometry and their placement). Since the unknown potential distribution is a function of many of the physiological components in blood and tissue, the primary modelling aim here was to, by simulation establish an adequate and identifiable functional relationship between this distribution and the level of cholesterol in the blood. This would then provide a unique 'impedance fingerprint' corresponding to a given cholesterol level.

2.4. Inclusion of particles in the problem domain

As mentioned before the human blood is a complex conductive medium. Fatty substances (lipids) are present in the plasma in suspension and in solution. Cholesterol, the particles used in this simulation study is almost insoluble in water (0.095 mg/l at 30 °C) and it is transported in the blood stream by lipoproteins (made up of proteins and lipids) that are water-dispersible and carry cholesterol and triglycerides internally. Based on the size, lipoproteins vary from chylomicrons (100-1000 nm in diameter), very low density lipoprotein (VLDL, 30-80 nm), intermediate density lipoprotein (IDL, 25-50 nm), low density lipoprotein (LDL, 18-28 nm) and high density lipoprotein (HDL, 5-15 nm). LDL-bound cholesterol is referred to as 'bad cholesterol' because high LDL level (in concentration and smaller particle size) is linked to cardiovascular diseases. On the other hand, HDL-bound cholesterol is often termed 'good cholesterol' because HDL can remove cholesterol from cells and atheroma and transport it back to the liver. Triglycerides, which form major components of VLDL and chylomicrons are also linked to cardiovascular diseases. Hence the Total cholesterol in the blood is defined as the sum of HDL, LDL, and VLDL. Given the wide variations in size and density of lipoproteins and the concentration of cholesterol they contain, it should be possible to measure by impedance technique not only the Total cholesterol but also its constituent components. Furthermore, these particles provide high contrast ratio in terms of electrical properties compared to other components in the blood. For example, because of different water content blood has a resistivity of about 1.6 Ωm, whereas fat has a resistivity of about 25 Ωm – 15 times higher than blood. Tissues other than those of heart and lungs have an approximate resistivity of 10 Ωm.

From the modelling point of view it is important to note that total cholesterol of 5 mmol/l corresponds to about 10^{12} lipoprotein particles (5-30 nm in size) in each mm^3 of blood. This clearly poses a major challenge for taking into account every individual particle for modelling purposes. This would not only introduce enormous complexity in building FE models but also dramatically increase modelling times to an unacceptable level.

This problem was tackled by using a particle aggregation (coagulation) strategy in which smaller number of larger particles, N_c was used keeping the total volume of cholesterol particles, V_c, corresponding to a given blood cholesterol level constant. Knowing the total volume of cholesterol in 1 mm^3 of blood plasma, the total volume of cholesterol in the blood volume, V_b being modelled can be calculated. These parameters were then adjusted for FE models in two dimensions. However, this simplifying modelling strategy needed to be quantitatively justified by modelling experiments. This was to establish the maximum number of cholesterol particles above which no significant change in the modelling results could be obtained by further increasing the number of particles. Furthermore, the effects of randomness in the distribution (placement) of these N_c particles on modelling results also needed to be quantified. As it is evidenced from some of the modelling results given below in Section 3 this strategy for particle aggregation (coagulation) simplifies FE models (Figure 3) without significantly affecting the results of FE modelling. Figure 4 shows typical FE discretisation used at the individual particle level. For simulation runs, the random distribution of particles in the active volume was achieved at the pre-processing stage by using appropriate Matlab scripts interfacing the FE software package COMSOL. This allowed automatic random generation and placement of particles in the problem domain for subsequent FE discretisation.

Figure 3. 2D FE models showing variable number of particles, N_c between the driving electrodes.

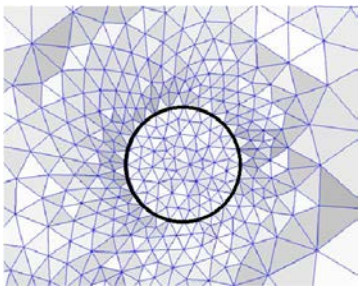

Figure 4. Details of 2D finite element discretisation in and around a single particle.

3. Some of the modelling results and discussions

3.1. Comparison with simple analytical solutions

To test the 2D FE models, a number of simple cases were tested for which accurate analytical solutions exist. Figure 5 shows the two cases in which 3 impedances are placed in series and in parallel occupying fully the problem domain between the electrodes. More realistic cases for this are

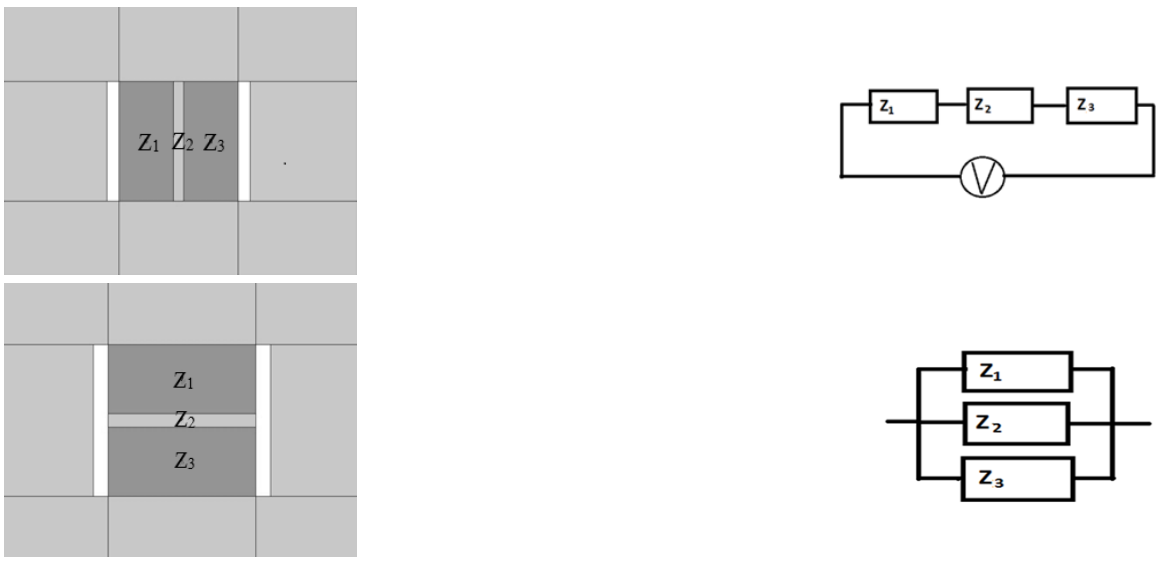

Figure 5. Simple series (above) and parallel (below) placement of impedances and their FE models.

shown in Figure 6 in which spherical particles are placed in series and in parallel with the driving electrodes. FE modelling results for these cases gave good agreement with those obtained from analytical calculations.

Figure 6. Series (left) and parallel (right) arrangements of particles in FE models for comparison with simple analytical solutions.

3.2. Effects of the number of particles, N_c and their distribution

For total volume of cholesterol particles, V_c corresponding to a given cholesterol level (3 mmol/l) the effects of particle numbers, N_c are shown in Figure 7. It shows that above a given threshold (N_c≈200-300, further refined to 500 by 3D modelling) no appreciable change in the modelling results can be obtained. This justified the particle aggregation strategy discussed in Section 2.

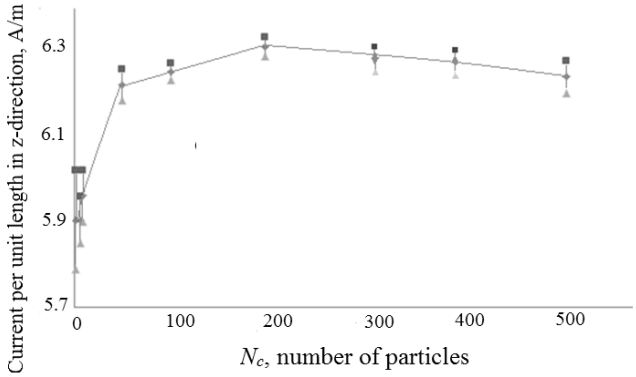

Figure 7. Variation of modelling results with number of particles, N_c used in 2D FE modelling (total volume of particles, V_c=const.).

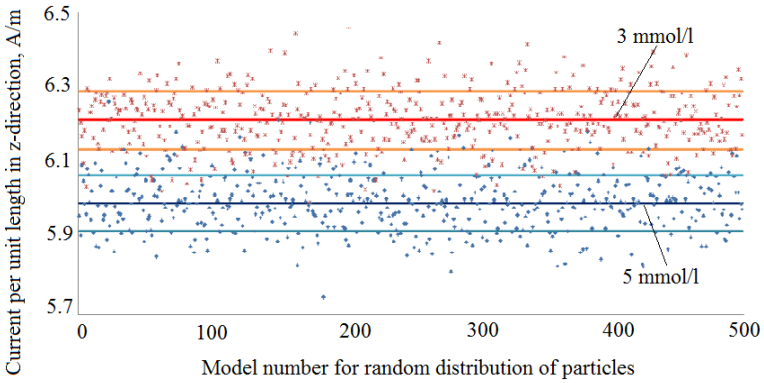

Figure 8. Effects of the distribution (placement) of particles on modelling results for 500 FE models containing randomly distributed particles (total number of particles, N_c=200=const.).

Figure 8 presents the effects of particle placement on modelling results which essentially shows that for a threshold number of particles, N_C the effects of placements of particles on modelling results average out to a clearly identifiable value corresponding to a given cholesterol level.

The most important consequence of the above two graphs is that despite the enormous number of cholesterol particles in a given volume of blood there exists a much smaller threshold number of particles which is enough to simulate the effects of these larger number of particles. Furthermore, for this threshold number of particles the effects of their random distribution averages out.

3.3. Fringe field effects

Figure 9 shows the fringe field effects at the edges of driving electrodes which justify the extension of problem domain beyond that bounded by the electrodes. This points to a need for 3D modelling since such effects are also present in the *z*-direction. The fringe field effects can be minimised in practice by effective screening which is well practiced in other areas.

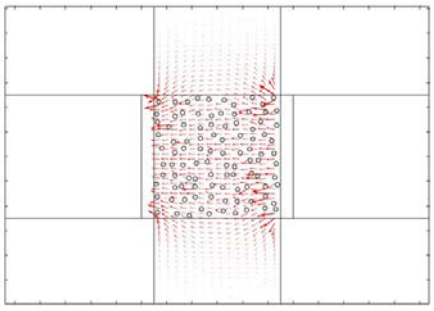

Figure 9. Fringe field effects at the edges of driving electrodes for a given distribution of particles (the arrows represent current density vectors **J**).

3.4. Effects of cholesterol level

The 2D FE modelling results presented in Figure 10 show that the impedance technique can be used to differentiate between different levels of cholesterol in the blood. However, they also point the need for accurate 3D FE modelling to refine these results and to take into account some of the important '3D effects'.

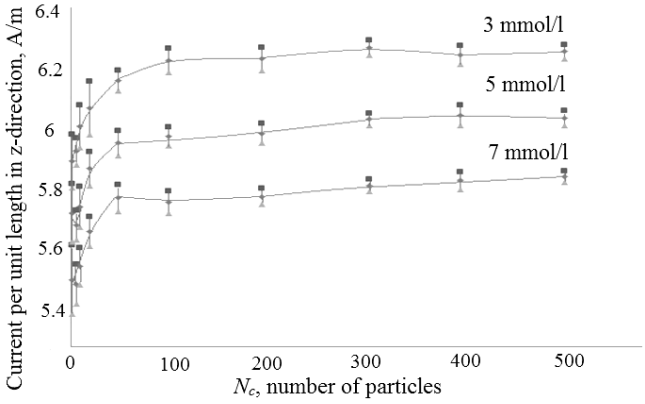

Figure 10. Electrical 'fingerprints' corresponding to different cholesterol levels (total volume of particles, V_C=const. for a given cholesterol level)

4. Conclusions

From the 2D modelling results presented this paper the following main conclusions can be made: (a) noninvasive impedance measurements can be used to differentiate between levels of Total cholesterol

in blood, (b) this is based on distinct electrical 'fingerprints' mentioned above, (c) detail 3D FE modelling is needed to take into account some of the electrical effects which cannot be seen in 2D.

This work is on-going and the focus of the current research is to incorporate in the accurate 3D FE models major blood components and quantify their effects.

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