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Non-invasive measurement of cholesterol in human blood by impedance technique: an investigation by 3D finite element field modelling

Ekaterina Aristovich and Sanowar Khan

City University London, School of Engineering and Mathematical Sciences,
Northampton Square, London EC1V 0HB, UK

E-mail: Ekaterina.Aristovich.1@city.ac.uk

Abstract. This paper concerns detection of particle concentration (e.g. cholesterol) in conductive media (e.g. human blood) by impedance technique. The technique is based on changes in the impedance measurement across a given conducting medium due to changes in the particle concentration. The impedance is calculated by calculating the current through the conducting media produced by electric field distribution between two electrodes. This is done by modelling and computation of 3D electric fields between the electrodes for known voltages applied between them using the well-known finite element method (FEM). The complexity of such FE models is attributed to particle distribution, their geometric and material parameters, and their shape and size which can be of many orders of magnitude smaller than the overall problem domain under investigation. This paper overcomes this problem by adopting an effective particle coagulation (aggregation) strategy in FE modelling without significantly affecting the accuracy of field computation.

1. Introduction

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) [1-3] and quantitative analyses (BMI, fuel purity, impedance spectroscopy) [4-8]. Modelling of non-conductive particles in conductive solution has been studied for several decades. There are in existence analytical formulas and methods for modelling separate particles, particles with effective conductivity [4, 5] as part of various sub-modelling approaches. The strategy adopted in this paper is instead of taking an effective conductivity in a volume of interest, it is possible to introduce an effective aggregation scheme by which small particles are aggregated together to reduce scaling factor without significantly decreasing the FE solution accuracy (especially for high aspect ratio of particle/media conductivities) the problem.

2. Particles suspended in conductive media

The mathematical modelling methodologies developed in this work have been applied to non-invasive detection of cholesterol particles in human blood by impedance technique. This points to the development of a simple, non-invasive method for measuring total blood cholesterol in which the conductivity distribution of objects (e.g. cholesterol particles carried by lipoproteins) within a test volume (e.g. blood plasma) is measured in the form of electrical impedance. 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) [9]. This means from the electric field and conductivity point 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 very different from those of blood plasma, which contains no cells [10, 11].

Cholesterol is almost insoluble in water and it is transported in the blood stream by lipoproteins that are water-dispersible and carry cholesterol and triglycerides internally. It is important to note that a total cholesterol of 5 mmol/l corresponds to about 10^{12} lipoprotein particles (5-30 nm in size) in each mm^3 of blood. At the same time cholesterol particles have the highest contrast ratio in terms of electrical properties among other components in a given blood volume. This clearly shows a major challenge in taking into account individual particles for modelling purposes which would introduce enormous complexity and dramatically increase modelling times to an unacceptable level.

3. Mathematical models and its finite element realisation

3.1. Field modelling and impedance calculation

For a given potential distribution φ on the electrodes (Figure 1) the electric field distribution in the 3D problem domain $\Omega(x, y, z)$ between the electrodes is given by the following Laplace's equation:

$$\nabla^2 \varphi = 0 \text{ in } \Omega \quad (1)$$

Under appropriate boundary conditions shown in Figure 1 the above equation is solved by finite element method (FEM) [12] in terms of electric potential φ for given conductivity (σ) and permittivity (ϵ) distribution 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) and $\mathbf{D} = \epsilon \mathbf{E}$ 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:

$$Z = \frac{V}{I} \quad (2)$$

With frequencies lower than 100 kHz most living tissues are assumed being electrolytic conductors. At higher frequencies the dielectric properties of bio-tissue may dominate. The higher the frequency the closer tissue properties come to those of water. For the modelling studies the above field equation was solved using the commercial software package COMSOL [13].

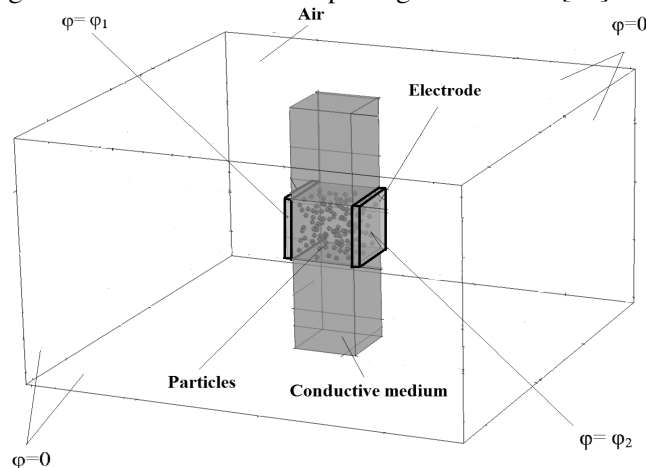


Figure 1. Basic 3D finite element (FE) model of particles in a conductive medium.

3.2. Finite element (FE) models

In order to tackle the problem defined above, full 3D FE modelling of current and potential distribution is required as the current is not confined to the measurement plane between the electrodes and changes in conductivity off this plane also contribute to calculated potential data. However, in order to establish confidence on some of the initial modelling results a number of 2D FE models were also set up. The basic 3D model used for simulation studies is shown in Figure 1 which shows the ‘active’ conductive medium between the electrodes (e.g. blood plasma, etc.) and beyond to account for any fringe field effects. In the absence of significant fringe field effects it can be assumed that only particles suspended between the electrodes contribute to the change in impedance between the electrodes. It also shows the boundary conditions under which equation (1) by FEM. Some of the initial 3D models were tested by comparing their results with those from corresponding 2D models with limited number of particles for which analytical results exist. This not only, to a certain extent establishes confidence on the on the 3D models but also justifies their use for subsequent simulation studies for realistic material and geometric properties.

3.3 Introduction of particles

For a given total cholesterol value it is not difficult to calculate the total volume of cholesterol particles V_c that would occupy a given volume of blood V_b in between the electrodes in Figure 1. The radius of each of the cholesterol particles r_c can then be calculated from the total number of cholesterol particles N_c contained in the volume V_c that need to be used for modelling purposes. However, as mentioned above it is not realistic and computationally efficient to do so in FE models because of the sheer number of particles that it represents. The alternative approach is to establish by modelling experiments the maximum number of cholesterol particles above which no significant change in the modelling results can be seen. This strategy of particle aggregation (coagulation) simplifies FE models (Figure 2) without significantly affecting the results of FE modelling. This can be clearly seen from Figure 3. In Figure 2 the same total volume of cholesterol particles V_c is represented by two different total numbers of particles, which are randomly distributed.

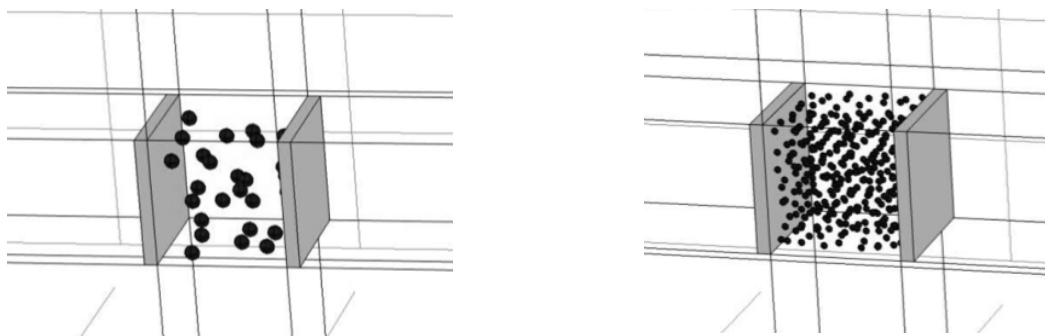


Figure 2. Approximation of a given total volume of particles by different particle numbers.

Figure 3 essentially shows that a given total volume of particles can be represented by variable number of particles and a threshold value of this number can be achieved ($N_c=500$) by FE modelling beyond which any further increase in the number of particles will not significantly affect the modelling results. This aggregation approach significantly reduces modelling complexity and save considerably computation time.

It should be noted that for each of the particle numbers used in Figure 3, modelling results were obtained for 10 different random distributions of these particles to quantitatively ascertain the effects of particle distribution on modelling results. Hence the upper and lower bounds of currents I for each

of the particle numbers used for FE modelling. As can be seen the effect of the distribution of particles on modelling results decreases as the total number of particles increases.

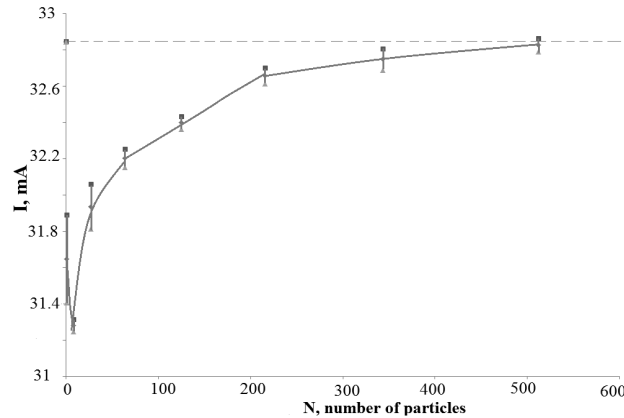


Figure 3. Number of particles used in FE models against modelling results (e.g. total current I between the electrodes, $V_c = \text{const}$).

4. Comparison of simplistic 3D modelling results with corresponding analytical results

Because of the complexity of 3D FE models involving a large number of particles in a conductive medium some of the initial modelling studies were carried out for simplistic conductivity distributions in the problem domain for which analytical solution and 2D modelling results exist.

4.1. Parallel cylinders and spherical particles aligned horizontally and vertically

It is clear that for FE modelling a given arrangement of spherical particles in 3D can be simulated in 2D by considering the particles are ‘cylinders’ extended infinitely in the z direction. A 3D equivalent of this 2D model would be cylinders of finite z -direction dimension in a 3D problem domain represented by the first set of models in Figure 4. The second set of models in Figure 4 shows similar arrangements for particles arranged vertically. So a 2D model with particles arranged vertically or horizontally equivalents to a corresponding 3D model with cylinders (which model the particles in 2D) arranged in the same way. The current values obtained from modelling of these scenarios are given in Table 1 below. As expected, a vertical arrangement of cylinders between the electrodes offers maximum ‘resistance’ to current paths.

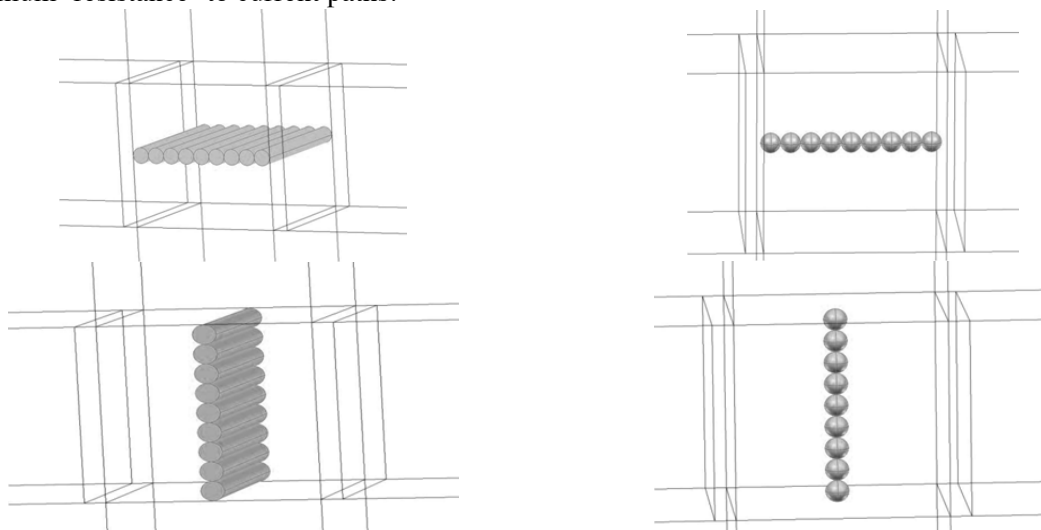


Figure 4. 3D equivalents of 2D models of particles (left) and their realistic 3D models (right).

Table 1. FE modelling results (calculated currents in mA) for cases shown in Figure 4

	3D equivalents calculated from 2D models	Cylinders in 3D models	Spherical particles in 3D models
Horizontally arranged	30.7	29.6	32.0
Vertically arranged	23.0	22.8	32.4

4.2. *Extreme cases*

Finally, two extreme cases were modelled in 3D: one with no suspended particles (Figure 5) and the other with one ‘large’ spherical particle equivalent in volume to the total volume of smaller particles suspended at the centre of the problem domain between the two electrodes (Figure 6). For the first case, it is expected to see the electric field and current density uniformly distributed in the volume between the electrodes, which can be seen in Figure 5. The theoretical value of this uniform current density ($J=976.8 \text{ A/m}^2$) agrees very well with that obtained from modelling (graph in Figure 5).

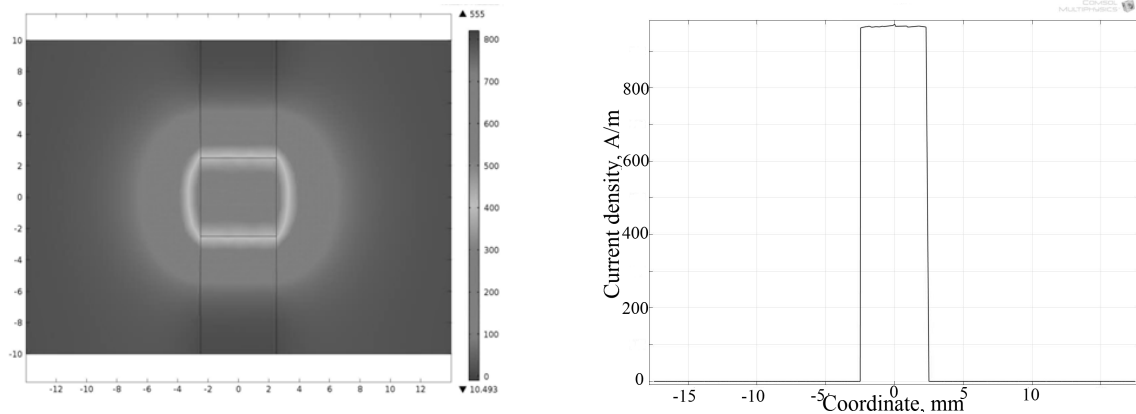


Figure 5. Electric field and current density distributions in the problem domain with no suspended particles.

Equivalent electric field and current density distributions for the second extreme case can be seen in Figure 6 below.

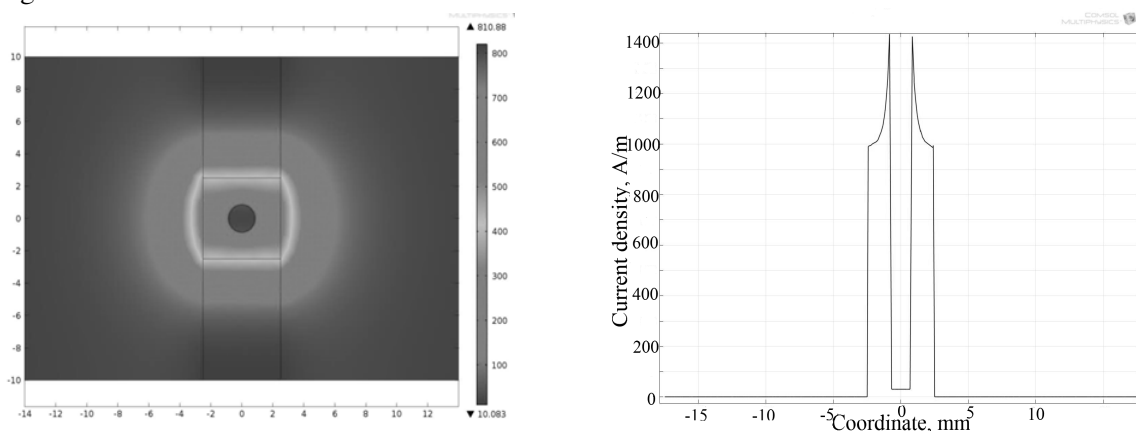


Figure 6. Electric field and current density distributions in the problem domain with one ‘large’ suspended particle placed at the centre of the problem domain between the electrodes.

The analytical current density values in the particle ($J_{sp}=20 \text{ A/m}^2$) and in the surrounding conducting medium ($J=1425.6 \text{ A/m}^2$) are in good agreement with those obtained from 3D FE modelling (graph in Figure 6).

5. Conclusions

Methodologies have been developed for FE modelling and computation of electric field distribution in conductive media containing suspended particles of various sizes, shapes and material properties. This has been used to model cholesterol particles in human blood which has so far shown encouraging results for detection of total cholesterol in the blood by impedance technique. This should ultimately lead to a practical device for non-invasive measurement of blood cholesterol.

Further work is being carried out to include even more blood components in the 3D FE models developed so far.

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