A hybrid FEM model to simulate the electrical characteristics of biological tissues at the cellular level

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Abstract. Cancer screening is possible with multi-frequency electrical impedance tomography since specific impedance variations are observable as a function of frequency. Through genetic mutations, malignant cells have different cellular characteristics than benign cells and a different impedance signature as a function of frequency. The objective of this project is to develop a FEM model to simulate the electrical characteristics of benign and malignant cells at the cellular level. Traditional tetrahedral element meshing techniques were first considered but the narrowness of the extracellular space and thinness of cell membranes made it impractical since the number of FEM elements quickly reached values that were computationally unmanageable on a typical workstation. We are therefore proposing a hybrid FEM model which combines a standard tetrahedral element meshing technique with 2D surfaces to model the extracellular fluid and discrete electrical components to represent cell membranes. The proposed hybrid modelling approach was used to develop a 3D FEM model of the skin with cellular-level details that can be used to better understand how impedance measurements performed on the skin are affected by lesions as a function of frequency as well as cellular geometrical and electrical parameters.

1. Introduction

Multi-frequency electrical impedance tomography (MF-EIT) has been proposed as a technique for cancer screening. Biological tissue identification is possible with MF-EIT since specific impedance variations are observable as a function of frequency. At lower frequencies, currents are generally constrained to the extracellular space since cell membranes exhibit high impedances. At higher frequencies, currents are free to flow through the cells since membranes have much lower impedances. Through genetic mutations, malignant cells have different cellular characteristics than benign cells such as increased nuclear to cytoplasmic ratios, larger cell volumes and wider extracellular spaces [1]. Malignant cells have therefore a different impedance signature as a function of frequency which allows MF-EIT to discriminate them [2].

The objective of this project is to develop a 3D FEM model to simulate the electrical characteristics of benign and malignant cells at the cellular level including nuclei, cytoplasm, extracellular fluid as well as nuclear and cytoplasmic membranes. Traditional tetrahedral element meshing techniques were first considered but the narrowness of the extracellular space and thinness of cell membranes made it impractical since the number of 3D FEM elements quickly reached values that were computationally unmanageable on a typical workstation. We
are therefore proposing a hybrid 3D FEM model which combines a standard tetrahedral element meshing technique with 2D surfaces to model the extracellular fluid which are interconnected to the tetrahedral mesh using discrete electrical components representing cell membranes. This hybrid modelling approach has been applied to malignant and benign cutaneous tissues to assess the applicability of MF-EIT to skin cancer screening.

2. Methods
As described in previous studies [3, 4], the proposed hybrid modelling approach is realized in two steps: macroscopic and cellular modelling. The complete macroscopic 3D hybrid model is obtained by subdividing the entire medium into subdomains each corresponding to a different biological tissue. For instance, the 3D skin model that will be presented in the next section

Figure 1. Cellular-level model. (a) Two adjacent cells. (b) Model of a section of the nuclear membrane bordered by a red dotted line in (a). (c) Model of a section of the cytoplasmic membranes and the extracellular fluid bordered by a black dotted line in (a).
has been subdivided into the following subdomains: *stratum basalis, stratum spinosum, stratum granulosum, stratum corneum*, the basement membrane and the dermis. The macroscopic model also incorporates different lesion types, such as *in situ* melanoma, malignant melanoma and dysplastic nevus as well as an electrode array. All FEM modelling was performed using the complete electrode model [5]. The anisotropic electrical properties of each subdomain was either obtained from the literature (*stratum corneum* and basement membrane) or from the cellular modelling approach described in the next paragraph.

A cellular-level 3D FEM model was assembled for each biological tissue as a 3D interlaced bricked segment of typical cells, two of which are shown in figure 1(a) and include the following cellular structures: nucleus, cytoplasm, extracellular fluid as well as nuclear and cytoplasmic membranes. The nucleus and cytoplasm were modelled using standard tetrahedral elements as represented in figure 1(a). In previous studies [3, 4], nuclear and cytoplasmic membranes as well as the extracellular fluid were also modelled using standard tetrahedral elements. Since these structures are very thin compared to the typical dimensions of a cell, this approach quickly lead to very large numbers of FEM elements that were unmanageable on a typical workstation. In the hybrid approach we propose, these structures are rather modelled by 2D surfaces and discrete electrical components. As represented in figure 1(b), nuclear membranes are modelled by electrical components which interconnect corresponding nodes from the nucleus and cytoplasm. As shown in figure 1(c), the extracellular fluid is modelled by a 2D surface subdivided in triangular elements. The nodes from these triangular elements are connected to corresponding nodes from the cytoplasm tetrahedral elements through discrete electrical components representing cytoplasmic membranes.

The electrical properties of each cellular structure were obtained from the literature [6] while geometrical properties were extracted from histological images obtained from a dermatopathologist. To obtain the anisotropic electrical properties of each biological tissue, the forward problem of EIT was solved on a 3D bricked segment of geometrically regular cells while applying a current in the longitudinal or transverse direction to simulate anisotropy. The computed voltages were then interpolated onto the vertices of a homogeneous mesh whose dimensions were the same as the 3D bricked segment. The inverse problem of EIT was solved on the homogeneous mesh to obtain the anisotropic electrical properties of each biological tissue that were then incorporated into the macroscopic model described above.

3. Results

The proposed approach was applied to develop a hybrid 3D cutaneous model including all skin layers and epidermis sublayers. The model includes two microinvasive electrodes and lesions such as an *in situ* melanoma, a malignant melanoma and a dysplastic nevus. Figure 2 shows transverse sections that were obtained at 500 Hz and 1 MHz in normal skin and with an *in situ* melanoma whose location is outlined by a black rectangle. Figures (a)-(c) show that at 500 Hz the current density below the basement membrane is quite low compared to 1 MHz (b)-(d). Figures (c)-(d) show that the current density inside the region corresponding to the *in situ* melanoma is higher at each frequency than in normal skin (a)-(b).

4. Discussion

The proposed hybrid modelling approach was used to develop a 3D FEM model of the skin with cellular-level details that can be used to better understand how impedance measurements performed on the skin are affected by lesions as a function of frequency as well as cellular geometrical and electrical parameters. This new approach makes better use of computing resources since it does not require meshing thin cellular structures with standard 3D meshing techniques that would increase the number of FEM elements by a factor of 1 to 10 thousands.
Figure 2. Transverse section of the skin model showing the modulus of the current density (A/µm²) distribution flowing between 4-mm-spaced electrodes identified by red arrows at 500 Hz (a)-(c) and 1 MHz (b)-(d). (a)-(b) show the current distribution in normal skin and (c)-(d), an in situ melanoma. The colour map is defined on a decimal logarithmic scale. The cutaneous lesion is outlined in black. The x-axis and y-axis are expressed in millimetres.

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