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ORIGINAL PAPER

The feasibility of computational modelling technique to detect the bladder cancer

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Abstract A numerical technique, finite element analysis (FEA) was used to model the electrical properties, the bio impedance of the bladder tissue in order to predict the bladder cancer. This model results showed that the normal bladder tissue have significantly higher impedance than the malignant tissue that was in opposite with the impedance measurements or the experimental results. Therefore, this difference can be explained using the effects of inflammation, oedema on the urothelium and the property of the bladder as a distensible organ. Furthermore, the different current distributions inside the bladder tissue (in histological layers) in normal and malignant cases and finally different applied pressures over the bladder tissue can cause different impedances for the bladder tissue. Finally, it is believed that further studies have to be carried out to characterise the human bladder tissue using the electrical impedance measurement and modelling techniques.

Introduction

The use of mathematical techniques (both analytical and numerical methods) in science and engineering is widely usual from the last few decades. However, in the biomedical field of study, both of these methods are used in order to understand the complex behaviour of the human body. One of these applications that can be designed to model the bioelectric phenomena of the body is the fitting of the Cole equation [1]. The complex electrical impedance of the living tissue was found in different organs and also different benign and malignant areas of living tissues to characterise them using this fitting programme. Also, some researchers reviewed the application of computing technology, numerical modelling methods such as finite element methods to evaluate the bioelectric properties of the living tissue [8]. They gathered the governing equations and then derived the finite element equations for the generalized bioelectric problem. Ohmine et al. (2000) designed a three dimensional finite element model of the breast tissue in order to analyse the predicted distributions of the electrical field and potentials [9]. They found that the model

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predictions agreed well with the experimental results and concluded that the bio impedance measurements technique may provide a non invasive method of breast cancer diagnosis. This numerical method has been applied to the cervical [11] and oesophagus [3] tissues to find their related electrical impedances to compare with the impedance measurement results in these organs [3,11]. They found some differences in the measured and modelled electrical impedance spectra of these tissues that may be explained by changes in the cell arrangements and their related extra-cellular spaces. It means that according to the comparison of Jones experimental and modelling results, the modelling outcomes confirmed the difference between the impedance of columnar and squamous tissues but the modelled impedance varied significantly depending on the amount of surface fluid present [3].

However, authors carried out a study about the bio impedance measurement of the bladder tissue [7] and introduced the electrical impedance spectroscopy as a new technique to detect of bladder pathology. Then, they modelled the current distribution inside the normal and malignant human urothelium and discussed about this modelled results according to the current distribution in different layers of the urothelium [4,5]. In this work, they did not explain any reason about the difference between the measured and the modelled results. Therefore, we are interested to evaluate the feasibility of computational modelling method to detect the bladder abnormalities in this study. In other words, to explain any possible problems and suggest their probable solutions in future studies to build suitable modelling structures.

Methods

Living tissue is inhomogeneous in structure and therefore in terms of electrical properties and numerical techniques this will be essential if it would be considered. It is clear from pathological textbooks that the human bladder tissue is constructed of transitional epithelium and has a highly anisotropic nature and it is composed of several layers such as superficial, intermediate and the basal layers as Fig. 1:

However, there is a difference between normal and malignant bladder tissue according to their morphological studies carried out by author. In their study, the normal and malignant cellular morphological parameters (intra and extra-cellular spaces of the human urinary bladder) were obtained from analysis of digital images of the bladder histology sections. Finally, the measured data showed that there is a significant difference between the cell dimensions (in intermediate layers) of normal and malignant bladder tissues [6].

Numerical method, finite element analysis was used to model the complex structures of the bladder tissue in this study (normal and malignant cases). This technique divides the volume into a many smaller volumes, named '*elements*' that are connected at '*nodes*', hence the name 'finite element' modelling. For this purpose, the cells were modelled as simple geometric shapes. Geometrical and physical parameters of the urothelium were used in this study to construct a high-resolution model of the cell. Geometric parameters, such as cell size were obtained from both literature and observation of histology sections for both normal and malignant tissues. For more information, one can refer to the study carried out by authors [6]. Currents were applied at the boundaries of the model in the x and z planes (i.e. parallel and perpendicular to the long axis of the cell, which is usually aligned parallel to the epithelial surface). The current distribution inside the bladder tissue, in every frequency was obtained using the FEA modelling technique. Therefore, the morphological parameters, the electrical properties and the measured impedance data were used to model the bladder tissue and then to find the current distribution inside the bladder tissue [4,5].

Electrical conductivities obtained from the cellular level models were assigned as material properties to epithelial layers in the macroscopic tissue model. This model consisted of three epithelial layers representing superficial, intermediate and basal cell types, underlying layers representing the basement membrane and connective tissue. Therefore, the macroscopic tissue model was constructed using the experimental morphological parameters for human bladder samples such as Fig. 2. There was no published data for the electrical properties of basement membrane, so models were solved using the published conductivity and permittivity values for the tendon [2].

The impedance value obtained is equivalent to a calibration factor, by which all raw modelled impedances can be divided to obtain impedivities in Ωm. It is therefore possible to directly compare plots of transfer impedivity against frequency (i.e. the impedance spectra) obtained from the model with those obtained experimentally for both normal and malignant cases. There is a study by authors that explains how we can measure the electrical impedance data of the human bladder tissue [7]. However, the current flowing through every node located on the boundary midway between the two drive electrodes can also be calculated and then integrated to give the total current flowing through each layer. Then, this information can provide an indication of the transfer electrical impedance of the bladder tissue in normal and malignant cases.

Results and discussions

After construction of the model and calculation of the current distribution inside the different layers of the bladder tissue [6], the real part of the complex impedance spectra modelled using parameters obtained for relaxed

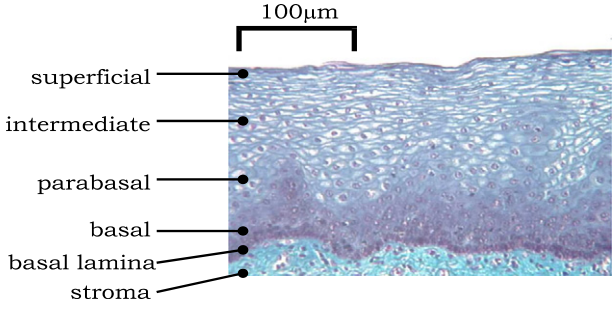

Figure 1 The micrograph of normal bladder tissue including different cell layers.

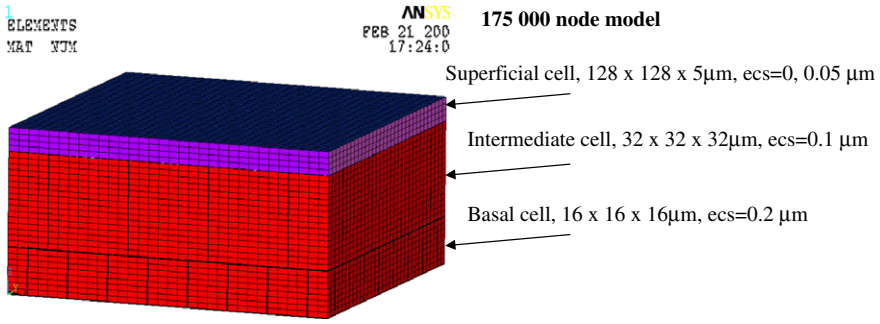

Figure 2 Macroscopic tissue model constructed from the literature using the morphological parameters of urothelium (ecs - = extra-cellular space).

human benign and malignant cells (*ex vivo*). The resulted impedance data from the modelling procedure was in the opposite situation to that reported by the measured data [10], where in the latter, the higher impedances were measured from abnormal tissue (see Fig. 3). The model results also suggest that impedance spectra associated with normal tissue structure are sensitive to the thickness of the mucus or fluid layer at the tissue surface, whereas those associated with abnormal tissue are not.

However, in constructing the computational models of the normal and malignant urothelium, due to the limited availability of data, we have had to make a number of assumptions about tissue structure and the electrical properties. For example, no information was available concerning the distribution of extra-cellular space in normal and abnormal urothelium, so we used those that had previously been used for models of normal and Cervical Intraepithelial Neoplasia (CIN) of the cervical epithelium. These values were based on measurements on high magnification micrographs published in the literature for squamous epithelia, and may not be relevant to transitional bladder epithelium. Surface plaques are not included in his model, and though these structures are extremely small, it is possible that they might influence the electrical properties of the tissue in a non-intuitive way.

Also, the model results showed that much of the injected current flows through the connective tissue beneath the urothelium [6]. Furthermore, there is no data available for the electrical properties of this layer, so data measured from the cervical stroma was used in this model, but may not be applicable to the bladder tissue, which contains a higher density of muscle that the cervical tissue. Modelling of other squamous epithelia (e.g. cervix) has shown that the changes in the impedance spectrum associated with neoplasia are primarily due to the increase in the volume of extra-cellular space and breakdown of surface tight junctions that are known to be associated with pre-cancerous changes. The fact that the measurements on bladder tissue yield the opposite results to those on cervix i.e. an increase in low frequency impedance for Carcinoma *In Situ* (CIS) compared to normal tissue suggest that: There is a reduction in the volume of Extra-Cellular Space (ECS) associated with CIS of the bladder, or the structure of the bladder tissue is significantly different to cervix in other respects, leading to a completely different distribution of current flow. In addition, it is much more difficult to obtain good quality, histological sections of the bladder epithelium, and in particular, there is little quantitative data available on the morphology of the stretched bladder tissue. It is virtually impossible to find information on the distribution of ECS in normal and CIS bladder, so it may be possible that the assumption that ECS increases with CIS,

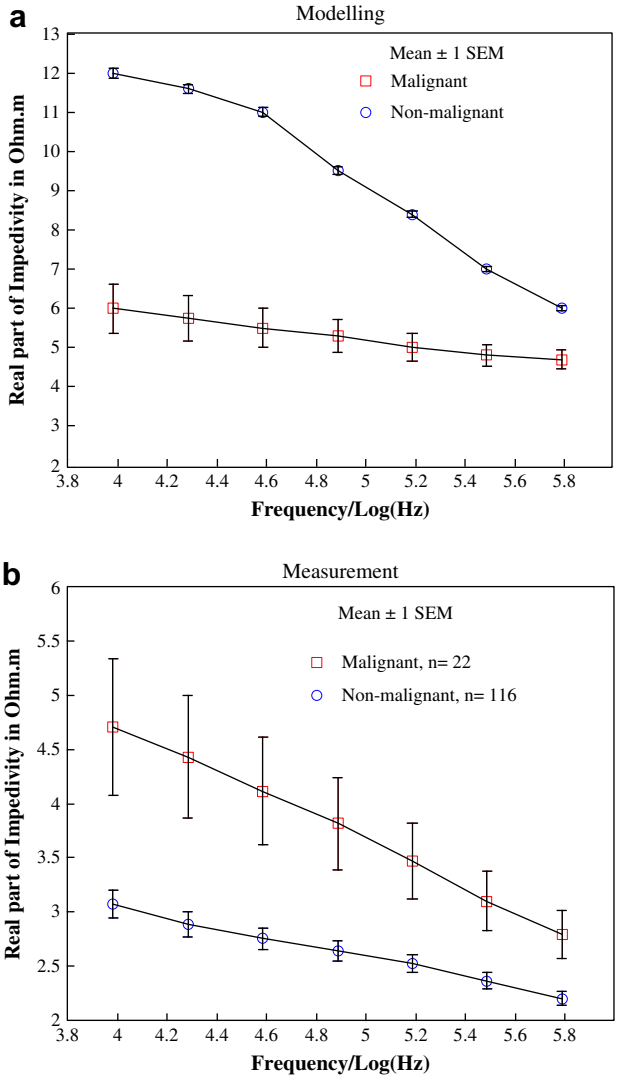

Figure 3 The real part of the complex modelled impedance spectra (a) and the measured impedance (b) for normal and malignant human bladder tissue.

which was made when constructing the computational models, may be incorrect, and hence at least partially explain the different results.

Bladder urothelium is also much thinner than cervical epithelium, which suggests that current flow in the lamina propria may be even more important than the current flow in the cervical stroma. The modelling information presented here focussed on changes within the urothelium only, assuming that the properties of the underlying tissue remain unchanged and therefore could not predict this result. According to the study carried out by Smallwood et al. in 2002, there is a significant effect of oedema and inflammation on the measured impedances [10]. Therefore, these factors do not affect the modelling results. Finally, the effect of the applied pressure over the probe in the impedance measurement method, is very important and this is neglected in the modelling procedure [6]. It is believed that if we consider the membranes parameters for our modelling method and hence we will have the capacitive components in this procedure. Then, it will be possible to have a good relation of impedivity to the frequency. However, we demonstrated that current densities showed small changes depend on frequencies at each surface layer thickness, thus, the impedivities considered to be shown small changes depend on frequencies [4,5]. Therefore, we will consider the effect of membrane in our modelling results in future studies.

Conclusion

Finite element analysis is a numerical method that allows us to improve our knowledge of current flow and gathering the bio impedance data in the living tissue. In this study, this method was applied to construct a model according to the data obtained from literature and measurements of histological sections of normal and malignant areas of the urothelium. Then, the real part of the complex modelled impedance data from the urothelium was calculated. The results of the models do not explain the measurements recorded *in vivo* and *ex vivo*. In conclusion, there are many factors, which may be in account for discrepancies between the measured and modelled data, and access to more comprehensive data on normal and transformed urothelial structure in the future may allow more accurate models to be developed. Some of these factors can be considered as the effect of inflammation and oedema on the measured impedance data, the distribution of current in different layers of the bladder tissue, the applied pressure over the measured probe and the effect of cell membranes on the modelling procedure. It is believed that the computational models may still play an important role in elucidating the differences in the measured impedance of the normal and malignant bladder tissue and hence can be realised as a minimally invasive technique to detect the bladder cancer.

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