Why is the measured impedance of the bladder tissue different from the computational modelling results?

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Abstract—**The electrical impedance spectroscopy technique was used to measure the electrical impedance of the human bladder tissue for differentiating pathological changes in the urothelium. Then, a numerical technique, finite element analysis (FEA) was used to model the electrical properties of this tissue in order to predict the impedance spectrum of the normal and malignant areas of this organ. After comparing the modelled data with the experimental results, it is believed that there are some factors that may affect the measurement results. Thus, the effect of inflammation, oedema, changes in the applied pressure over the probe and the distensible property of the bladder tissue were considered. Also, the current distribution inside the human bladder tissue was modelled in normal and malignant cases using the finite element analysis. This model results showed that very little of the current actually flows through the urothelium and much of the injected current flows through the connective tissue beneath the urothelium.**

Keywords— **bladder, computational modeling, electrical impedance measurement, normal, malignant**

I. Introduction

The finite element method has previously been applied to cervical and oesophagus tissues [1, 2]. Before the normal oesophagus changes to cancerous oesophagus, the tissue undergoes metaplasia from normal stratified squamous to a columnar epithelium. Differences in the electrical impedance spectra of the tissues appear to be explained by changes in cell arrangements and in the extra-cellular space. This suggests that an indication of tissue structure may be able to be derived from electrical impedance spectral measurements. Brown et al measured the electrical impedance of cervix tissue. According to their work, the measured electrical impedance made on normal squamous tissues was well separated from that made on pre-cancerous tissues [3, 4]. The impedance of normal areas was more than the impedance of abnormal areas. It was hypothesized that the characterisation of the electrical impedance spectrum of cervical tissue is related to cellular arrangements of the tissue. After that Walker et al. modelled the electrical impedivity of normal and pre-malignant cervical tissue using finite element analysis to find the related electrical impedance[4, 5]. Gonzalez-Correa et al (1999) measured the electrical impedance of the oesophagus tissue. They showed that the squamous and columnar tissues of the oesophagus could be separated by electrical impedance spectroscopy. Also, in this case, the impedance of normal areas was more than the impedance of malignant areas. They expected that it is possible to separate these tissue types using a data modelling process [6]. Then, D. M. Jones used finite element modelling to model the electrical properties of normal and pre-cancerous oesophageal tissue [1]. This modelling method was used to model the electrical properties of squamous and glandular columnar epithelia of the gastrointestinal tract in order to characterise the electrical properties of these tissues. The output from this model was compared with the measured impedance spectra. According to this comparison, the modelling 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 [1]. Keshtkar et al. measured the electrical impedance of the urinary bladder tissue and they found that the impedance of malignant area was significantly more than the impedance of the normal area [7]. Also, the finite element method was used to model the benign and malignant bladder tissue. Results of both measured impedance and modelling methods are in opposite each other. The impedance resulting from this model for malignant area was significantly less than the impedance of the normal area. We will realise this problem here.

II. Materials and methods

A. Electrical impedance measurement method

The electrical impedance of the human urinary bladder is measured at different frequencies according to the spectroscopy systems (the applied current to measure the impedance is very low). This constant current passed through two electrodes of a small sized probe that was designed and constructed by author [8]. These electrodes constructed of four gold wire electrodes, 0.5 mm in diameter, spaced equally on a 1.6 mm diameter circle. Total diameter of the probe was only 2 mm thus it was limited because of the maximum permitted diameter of endoscopic channel to pass the probe towards the inside of the urinary bladder during the bladder surgery. Detailed information about this probe can be found

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in Keshtkar et al in 2001 [9] and Smallwood et al in 2002 [10]. As we know, the most common form of measuring tissue impedance is the tetra-polar or the 4-electrode technique. In this technique, a known current is driven between two electrodes and the resulting voltage is measured between the other two electrodes. Therefore, the resulting potential was measured using this technique to obtain the impedance of the urothelium. In impedance data collection procedure, the probe regularly was calibrated using known conductivity of saline solutions before any measurement procedure to have the tissue impedance readings in terms of the impedivity in $\Omega.m$. The measured impedance data was recorded in a laptop in order for further data analysis. There is a study by author that explains how we can measure the electrical impedance data of the human bladder tissue in benign and malignant cases [7]. In addition, there is a paper from the author to relate the effect of inflammation and oedema on the resulting electrical impedance of the urinary bladder tissue in the form of increasing and decreasing of the related impedance respectively [10].

B. Finite element modelling method

For the purpose of modelling tissue structure, it is easier if cells are 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 the observation of histology sections [8, 11]. The normal and malignant cellular morphological parameters of the human urinary bladder were obtained from analysis of digital images of the bladder histology sections by the author. In this procedure, the mean value of cell sizes resulting from three areas (superficial, intermediate and basal layers) for malignant and benign groups was calculated. See A Keshtkar (2007) for more details about this imaging technique to calculate the morphological parameters [11]. 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, and a surface layer of variable thickness, representing a thin layer of mucus or surface fluid. Also, the macroscopic tissue model was constructed using the experimental morphological parameters for bladder samples. There is no published data for the electrical properties of basement membrane, so models were solved using the published conductivity and permittivity values for the tendon [12]. The conductivity of the underlying connective tissue was based on conductivity values previously measured from unfixed healthy cervical stroma [2] and permittivity published in the literature for uterus [12]. The mucus layer was assigned similar properties to those used for extra-cellular fluid. Current was applied to the drive electrodes in the macroscopic model in the frequency range 100 Hz- 10 MHz, and voltages calculated at the receiver electrodes in an identical arrangement to the *in vivo* tissue measurements. 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 impedivity against frequency obtained from the model with those obtained experimentally. Finally, the current flowing through every node located on the boundary midway between the two drive electrodes was calculated and then integrated to give the total current flowing through each layer. This information can provide an indication of the current distribution *in vivo*. Various model parameters can be altered at either the cellular or the macroscopic stage of the modelling process in order to assess the effect on the impedance spectrum or the current distribution. Models were solved with mucus layer thicknesses in the range 5 μm-100 μm.

III. Results and discussions

The real part of the complex impedance spectra of the human urinary bladder tissue was measured in different frequencies and is shown as Fig. 1.

There is inflammation and oedema effects on this measured impedance that the paper was published by author [10]. According to this study, inflammation will increase the related measured electrical impedance and oedema will decrease the electrical impedance. Therefore, these effects must be considered during the impedance measurements of

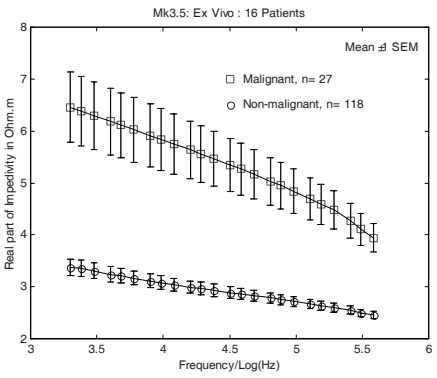

Fig. 1 Real part of impedivity versus log of frequency for normal and malignant bladder tissue [7]

the bladder tissue. Following this, the real part of the complex impedance spectra modelled using parameters obtained for relaxed benign and malignant cells parameters measured from histology sections are shown in Fig. 2a.

The effect of different mucosal layer thickness (in micrometers) on the normal impedance is also shown in this figure. Fig. 2b shows the same spectra, but in this case within the frequency range of the impedance measurement system. It can be seen that the model predicts impedance spectra that are within the same magnitude range as the data collected *in vivo* and *ex vivo*. However, the model predicts that at frequencies less than 100 kHz, impedances measured from benign tissue should be higher than those measured from malignant tissue. This is the opposite situation to that suggested by the measured data, where higher impedances are measured from abnormal tissue (Fig. 1). 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. We can gain a greater understanding of this behaviour by examining the current distribution in the normal and malignant models as following sentences. Fig. 3 shows the proportion of the total current flowing through each of the macroscopic model layers – surface fluid, superficial urothelium, intermediate urothelium, basal urothelium, basement membrane and connective tissue respectively, in the normal tissue model. Data is shown for a number of frequencies and for three thicknesses of the surface fluid.

Fig. 3b shows similar data for the malignant tissue model. It is immediately apparent that very little of the current actually flows through the urothelium itself (layer 2-4), but is divided between the surface fluid and underlying connective tissue at a ratio which depends on current frequency, depth of surface fluid and urothelial pathology. In the case of normal tissue, the presence of tight junctions and

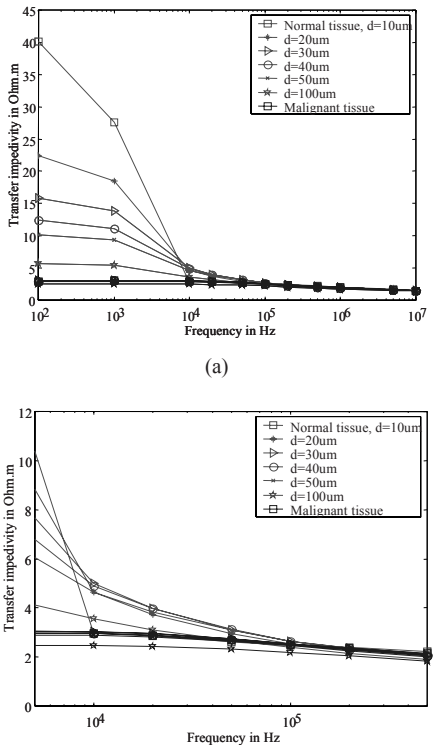

Fig.2 The real part of the complex modelled impedance spectra for normal and malignant urothelium

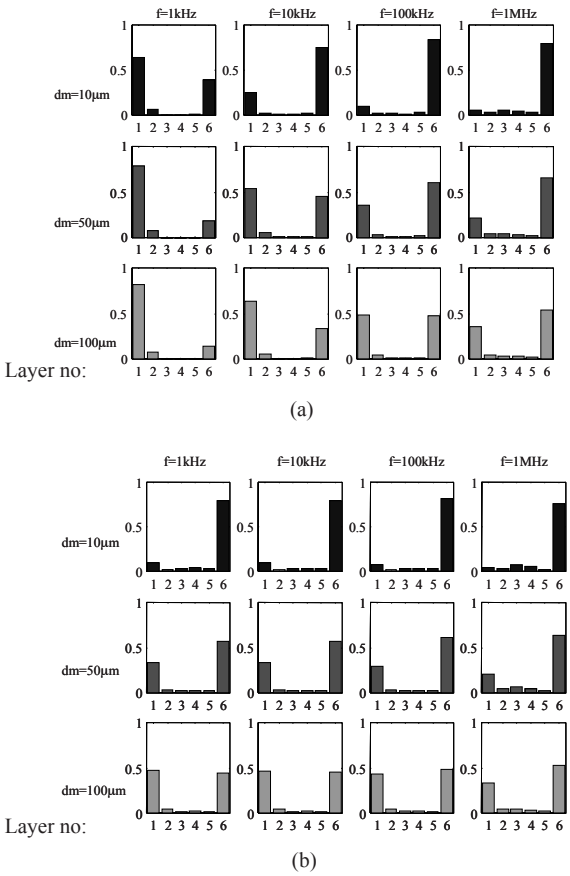

Fig. 3 Modelled current – depth distribution midway between drive electrodes for (a) normal tissue model, (b) Malignant tissue model at different frequencies and surface layer thicknesses (dm) Layer no. key: 1 – surface fluid, 2-superficial urothelium, 3-intermediate urothelium, 4-basal urothelium, 5- basement membrane, 6- connective tissue

narrow intercellular spaces forms a very high impedance barrier, and at low frequencies in particular, current is confined to the surface fluid. As the frequency is increased, the capacitive nature of cell membranes allows current flow into the surface cells, effectively 'short-circuiting' the tight junctions and allowing current to penetrate beneath the epithelium and into the relatively high conductivity connective tissue beneath, thus causing the characteristic drop in tissue impedance with increasing frequency. However, our malignant superficial cell models do not include tight junctions, and the extra-cellular space is also wider, so the barrier to current flow is greatly reduced, even at low frequencies. Fig. 3b shows that at least 50% of the injected current flows beneath transformed urothelium across the frequency range modelled. The results of the models do not explain the measurements recorded *in vivo* and *ex vivo,* where higher impedances were measured from tissue independently diagnosed as malignant, but are in agreement with measurements and models of other squamous epithelia, where malignancy results in a reduction in electrical impedance, Gonzalez-Correa et al. (2003), [13], [4]. Surface plaques are not included in this 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. The model results, Fig. 3, show that much of the injected current flows through the connective tissue beneath the urothelium.

Again, 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. Also, it is much more difficult to obtain good quality, histological sections of bladder epithelium, and in particular, there is little quantitative data available on the morphology of 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, which was made when constructing the computational models, may be incorrect, and hence at least partially explain the different results. The modelling information presented here focussed on changes within the urothelium only, assuming that the properties of the underlying tissue remain unchanged.

IV. Conclusions

Computational modelling is a technique that allows us to improve our knowledge of current flow in tissues, and hence electrical impedance methods as potential diagnostic techniques. Finite element models were constructed according to data obtained from literature and measurements of histological sections of normal and malignant areas of the urothelium. Then, the real part of modelled impedance spectrum based on models of normal and abnormal urothelium was calculated. The results of the models do not explain the measurements results. In conclusion, there are many factors, which may account for discrepancies between the measured and modelled data.

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