A HANDHELD ELECTRICAL IMPEDANCE PROBE FOR THE DETECTION OF MALIGNANT TISSUE

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Abstract: The electrical impedance of biological tissue is determined by the arrangements, shapes, and internal structure of the tissue cells. Measurement of this electrical impedance over a range of frequencies produces a characteristic spectrum which is dependent upon the physical structure of that tissue. A minimally-invasive hand-held device has been developed to measure such impedance spectra and hence to identify precancerous tissue, which differs histologically from normal tissue. The device transmits the results via a wireless link to a PC, providing an automatic and almost instantaneous assessment of likely tissue pathology. The initial results measured on cervical epithelium for the purpose of cervical cancer screening are presented here. The self-contained system is small, portable, and easy to use, and has been designed specifically for use in a clinical environment.

Introduction

Biological tissue consists of components which have both electrically resistive and capacitive properties, giving tissue a complex electrical impedance which is a function of frequency. The magnitude of the impedance and its frequency-dependence are related to the composition of the tissue, being affected by the arrangements, shapes, and geometric homogeneity of the tissue cells.

The electrical behaviour of tissue is dominated by different structures at different frequencies. At high frequencies ($\gtrsim$ 1 GHz) the flow of current through the tissue is dominated by its molecular structure, whereas at low frequencies ($\lesssim$ 100 Hz) the impedance is dominated by the electric charge which accumulates at large membrane interfaces.

At intermediate frequencies (sometimes referred to as the β dispersion region) the tissue impedance is largely determined by the structure of the cells. At lower frequencies within this range the current can be considered to pass mainly through extracellular space, *i.e.* around the outside of the cells, and hence the resistance to current flow is dependent upon the spacing and arrangement of the cells. At higher frequencies the current can penetrate the cell membranes, passing through both intracellular and extracellular space, and hence the impedance at these frequencies is also affected by the intracellular volume and, possibly, the size of the nucleus [1, 2].

Measurement of tissue impedance over the β dispersion frequency range produces a characteristic sigmoidal spectrum. The magnitude of the impedance is relatively large at low frequencies, but reduces and eventually plateaus at a smaller magnitude as the frequency is further increased. Figure 1 illustrates typical spectra for cervical epithelial tissue at a range of pre-cancerous stages. The data is derived from finite element (FE) computer models of the tissue and its response to an applied current [2, 3].

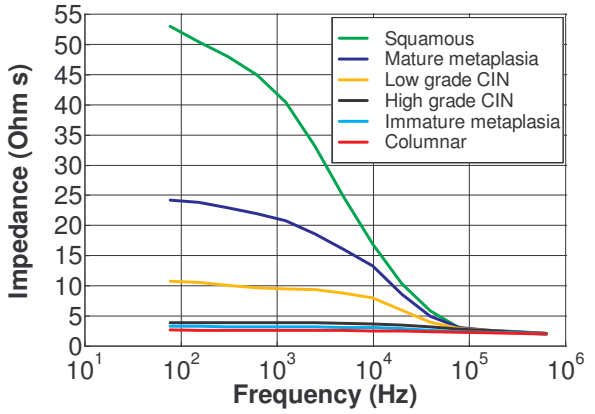

Figure 1: Characteristic electrical impedance (magnitude) spectra for cervical epithelial tissue

Diseases which affect the structure, shape, and arrangement of tissue cells produce a concomitant change in the electrical impedance spectrum of that tissue. It is therefore possible to distinguish between different tissue pathologies by measurement of the tissue impedance [4, 5].

The epithelial tissue of the cervix is a very structured, layered tissue which exhibits pronounced changes during precancerous development known as cervical intraepithelial neoplasia (CIN). Figure 2 shows a schematic illustration of the progression from normal cervical epithelium through to various stages of CIN. As the disease progresses the layer of flattened cells close to the surface depletes and the stratified arrangement of the tissue becomes less marked.

ISSN: 1727-1983

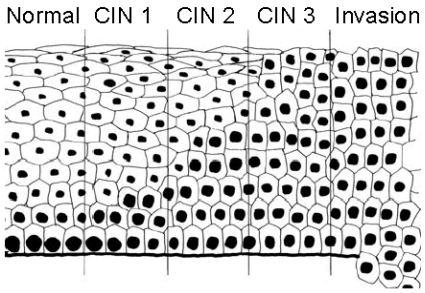

Figure 2: Schematic illustration of the progression from normal to precancerous tissue in cervical epithelium [2].

Previous studies (through both experiment [4, 5] and finite element computer modelling [3]) have shown that as CIN develops so the low-frequency impedance of cervical epithelium falls significantly. This is illustrated in Figure 1 for healthy tissue and tissue at various stages of CIN. It has been demonstrated that good separation between normal and precancerous tissue can be achieved by examination of the electrical impedance spectra [4, 5].

A prototype 'pencil probe' for measuring the electrical impedance of cervical epithelium has already been reported [4, 5]. This impedance spectrometer was found to be a potentially promising screening tool for cervical cancer, with a sensitivity and specificity similar to or better than present screening tests but with the advantage of producing results much more rapidly [5].

The original probe used in these studies contained four electrodes which were placed in direct contact with the tissue to be measured. A small electric current was then passed between one pair of electrodes and the resulting voltage measured across the second pair, from which the transfer impedance of the tissue was calculated. This procedure was repeated at eight frequencies from 4.8 kHz to 614 kHz. The hardware for this design was based on a single channel of the Sheffield Mk3 electrical impedance tomography (EIT) imaging system. Later developments to the probe increased the frequency range from 2 kHz to 1.6 MHz, basing the hardware on a single channel of the Sheffield Mk3.5 EIT system [6].

However, in clinical use, these prototype impedance spectroscopy systems proved to be a cumbersome set of equipment. The electrodes in the probe were physically connected by wire to a measurement box containing the controlling electronics, which in turn was physically connected to a computer (PC). The PC provided the user-interface for the system and a means to save the data, and was also used for later off-line (post-measurement) analysis of the data.

The system relied on a certain degree of user-expertise during the collection of the data, as it was necessary for the operator to judge when to record a reading based upon a continuous real-time display of measured impedance. Additionally, the agility and mobility of the operator was significantly limited by the necessary physical connection between the measurement probe and the computer.

This paper describes the development of this impedance spectroscopy system into a practical instrument designed specifically for use in a clinical environment. The new design incorporates a wireless link for communication between the probe and the PC, thus allowing the examination and measurement process to be unhindered by unwieldy physical connections. The system also incorporates an automatic acquisition process which eliminates the requirement for the user to operate the computer whilst simultaneously manipulating the impedance probe, and minimises the user-expertise required to record and interpret the results. As the probe system has been designed for the express purpose of measuring epithelial tissue, it has been named an "epitheliometer".

Materials and Methods

Measurement Procedure: With the new epitheliometer system, the clinician initiates a measurement via a touch-sensitive switch on the probe casing, having positioned the tip of the probe shaft against the tissue to be evaluated. The probe then takes multiple consecutive measurements of complex tissue impedance over the frequency range 76.3 Hz to 625 kHz, and performs checks on the quality of the data and the stability of the reading. The measurement cycle is automatically aborted after 10 seconds if the collected data does not meet preset target criteria. Otherwise, once a valid measurement of acceptable quality has been obtained, the probe automatically saves the result and transmits the data across a wireless link to a PC. The probe can now be used to take further impedance measurements at additional locations on the tissue if required.

Once the pre-specified (configurable) number of measurement locations have been examined, the PC software automatically analyses the data and provides an instant assessment of the likely tissue pathology at each point. The result is displayed to the clinician via a simple graphical user interface (GUI) on the PC. The system has been designed such that all communication between the probe and the PC occurs automatically, thus freeing the clinician to concentrate on the examination of the patient and not on the operation of the computer.

System Hardware: The epitheliometer impedance probe is a hand-held device with an extended shaft, as shown in Figure 3. The main body of the probe - which forms the handle - is constructed from translucent plastic, and contains the majority of the electronic circuitry which controls the operation of the device. Four gold electrodes positioned flush on the end face of the probe shaft allow a four-point impedance measurement to be performed. To reduce unwanted stray capacitance and improve the signal quality some of the electronic hardware has also been placed inside the probe shaft itself, close to the measurement electrodes.

The unit is powered by a rechargeable 3.6 V cell inside the probe handle. This cell is recharged by an inductive charger on which the probe stands when not in use. As the charger relies only on magnetic coupling and does not require any direct electrical contact with the probe, all the electronics can be contained within a fully sealed probe casing.

ISSN: 1727-1983

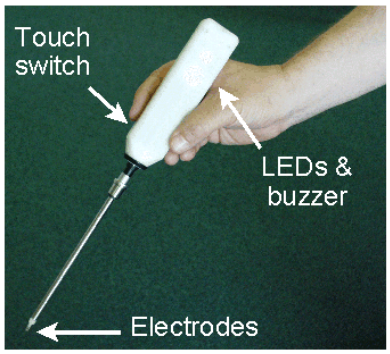

Figure 3: Photograph showing the hand-held wireless electrical impedance spectroscopy probe.

The behaviour and functions of the epitheliometer are governed by a microcontroller integrated circuit situated inside the probe. During the measurement procedure a sinusoidal current (3 μA peak to peak) is passed through the tissue between two of the electrodes which are configured as a current source and sink. This current through the tissue impedance causes a voltage to be developed across it which is measured using the second pair of electrodes. The resulting voltage is amplified and then demodulated in turn to give both the real and imaginary parts of the signal. An analogue to digital converter (ADC) is used to input the signal to the microcontroller where it is temporarily stored in memory. The microcontroller then initiates a new measurement cycle at the next frequency. Once measurements have been performed at all fourteen frequencies (76.3 Hz to 625 Hz in octave intervals) the microcontroller is responsible for analysing the data, verifying that it lies between predefined limits. The variance of consecutive measurements must also be acceptably small to ensure that the reading is stable and free from movement artefacts. If the data meets these criteria the result is stored in electrically erasable programmable read-only memory (EEPROM). The probe is now ready to take another measurement at the next location if desired.

Any data which is stored in the EEPROM is automatically transmitted across a wireless link whilst the probe is inactive. A radio frequency (RF) transceiver module in the probe receives data from the microcontroller and transmits it to a similar module situated in a purpose-built basestation. PC software then controls the transfer of data from the basestation to the PC via a universal serial bus (USB) connection.

System Software: The PC software provides an intuitive GUI to the epitheliometer system. The user is guided through the measurement process by the use of standard-style menus and pop-up boxes which prompt for specific inputs.

When the software obtains measured impedance data via the wireless link it immediately acknowledges its receipt to both the user and the probe. The data is then analysed by comparing the measured impedance spectrum with several predefined template spectra. The templates were determined from the electrical behaviour of finite element models of cervical tissue with different pathologies. The software classifies the tissue according to the probability that it fits each of the six template categories, which range from normal squamous tissue to high grade CIN. The resulting assessment is automatically displayed in a clear graphical format once all the measurements have been completed, without the need for any additional commands from the user. The complete measurement process including the data recording and analysis takes only a small number of seconds per tissue location.

Probe Sterilization: As the electrodes and shaft of the probe are necessarily in direct contact with tissue, care must be taken to prevent patient-patient cross-infection. Three alternatives are proposed to address this issue: a novel single-use membrane sheath which is electrically conductive but is impermeable to viruses [7], fitted over the probe shaft; a single-use disposable probe tip; or a reusable detachable probe shaft which can withstand autoclave sterilization. The latter is pictured in Figure 3.

Results

The performance of the new epitheliometer system has been validated by experimental measurements. The impedance of a known electrical circuit with a complex frequency-dependent impedance was measured using both the new system and the previous design, and the results compared against the expected theoretical spectrum. The test circuit comprised of a 1.2 kΩ resistor in parallel with a series 120 Ω resistor and 10 nF capacitor; these parameters were chosen to approximate the behaviour of normal squamous tissue.

Figures 4 and 5 respectively show the real and imaginary components of the impedance spectra, measured experimentally with the new epitheliometer system (pink) and the previous design (green), and also calculated mathematically using the known component values (blue). The experimental systems were each calibrated against a resistor of known value (1 kΩ). The data shown is the mean average of 100 consecutive measurements in each case.

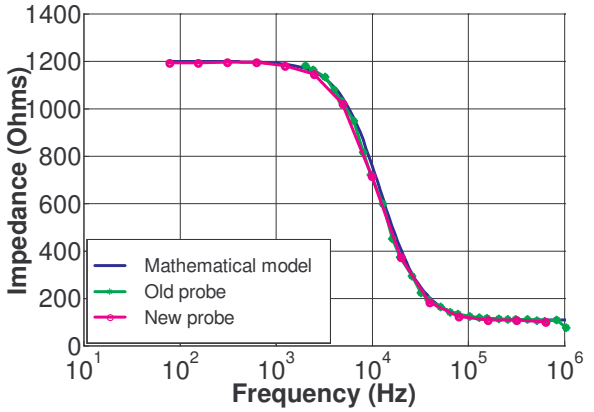

Figure 4: Real component of impedance spectra: comparison of performance between the new probe system (pink), the previous design (green), and the expected mathematical result (blue)

ISSN: 1727-1983

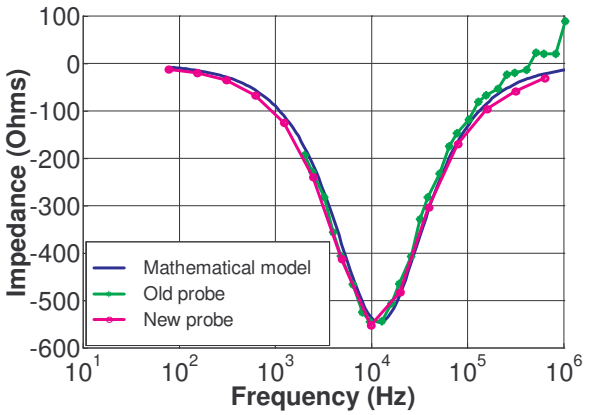

Figure 5: Imaginary component of impedance spectra: comparison of performance between the new probe system (pink), the previous design (green), and the expected mathematical result (blue)

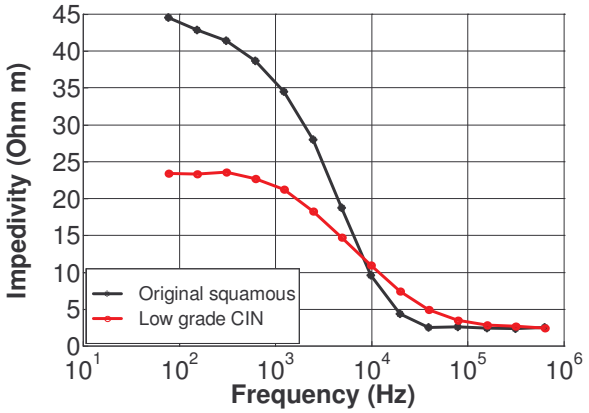

Figure 6: Preliminary clinical data: real component of impedivity spectra for original squamous epithelium (black) and low grade CIN (red)

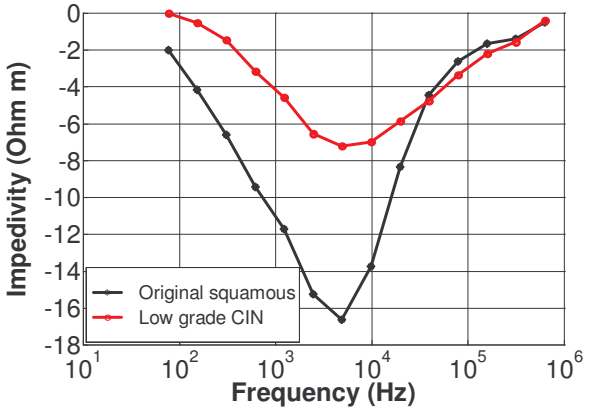

Figure 7: Preliminary clinical data: imaginary component of impedivity spectra for original squamous epithelium (black) and low grade CIN (red)

The close agreement between the data sets shown in Figures 4 and 5 indicates that the new epitheliometer system will reliably measure complexes impedances over its full frequency range, and that its performance is comparable to that of the previously reported system.

The epitheliometer has also been used to take preliminary clinical *in vivo* measurements on cervical epithelial tissue. These measurements were made in a colposcopy clinic after the study had been approved by an ethics committee and informed consent was obtained from the subjects.

The system was calibrated against a saline solution of known electrical resistivity (10 Ωm). Figure 6 shows the real component and Figure 7 the imaginary component of two typical impedivity spectra measured at different tissue locations on the same subject. One of the locations was judged by colposcopy to be original squamous epithelium tissue, and the other to have developed into low grade CIN; these correspond to the black curve and red curve respectively in Figures 6 and 7.

It can be seen that the impedance spectra for the two tissue pathologies differ significantly, as would be expected from previous studies [4, 5]. The improved frequency range (down to 76.3 Hz) of the new epitheliometer gives even clearer separation between the real components of the impedance spectra.

Discussion

The hand-held electrical impedance probe which has been developed offers significant improvements in usability over the original design described in [4]. The new probe incorporates a wireless communication link between the measurement device and the computer, and has built-in intelligence to perform automatic data acquisition, quality assessment, and analysis. The user needs only to execute a single button-press on the probe in order to perform an impedance measurement and be presented automatically with a likely assessment of the tissue pathology. The wireless design of the epitheliometer also reduces the risk presented to patients in the case of an electrical fault, since the device is battery-powered and electrically isolated. The use of multiple detachable probe tips eases the sterilization procedure and reduces the turnaround time between patients. The results of the epitheliometer have been verified experimentally against the previous system and against a circuit whose frequency-dependent behaviour was previously known. Clinicians have reported that the new epitheliometer is easier and quicker to operate and manipulate than the previous system.

The present application for the epitheliometer impedance probe is for patients who have been referred to a colposcopy clinic, although it would also be suitable for use in health clinics or general practitioners' surgeries. The small, portable, and relatively cheap nature of the system could enable the establishment of cervical screening programmes where they would otherwise not be feasible.

ISSN: 1727-1983

Significantly, use of the epitheliometer is not confined to just cervical tissue. The device provides a novel tool for investigating the behaviour of a range of healthy and diseased tissues, both *in vitro* and *in vivo*, and furthering the research into electrical impedance techniques.

Conclusions

A wireless handheld probe has been developed specifically for use in a clinical environment. The probe performs minimally invasive *in vivo* electrical impedance measurements for the detection of precancerous tissue. It provides an almost instantaneous measurement and assessment procedure, and thus assists the clinician to make a more informed diagnosis of tissue pathology. The wireless and automatic nature of the probe make it easy to manipulate during examinations and reduce the user-expertise required to record and interpret the results.

Acknowledgements

This research was funded by the New and Emerging Applications of Technology (NEAT) programme of the UK National Health Service.

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ISSN: 1727-1983