ORIGINAL ARTICLE

Development of Multi-frequency Electrical Impedance Spectroscopy (EIS) System for Early Detection of Breast Cancer

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Abstract

Breast Cancer is among the top five causes of cancer death and the topmost cause among women worldwide. The early diagnosis through simple, non-invasive and inexpensive screening can provide great deal of aids. Multi-frequency Electrical Impedance Spectroscopy (EIS) is quite attractive in this context as the instrumentation is relatively simple and research has demonstrated application in breast cancer screening. Considering the socio-economic status of developing countries like Bangladesh, a low cost reliable system is required that could be maintained and repaired by locally trained manpower. However limitation of local availability of even quite basic electronic component is another challenge. This paper focuses on the design and construction of multi-frequency EIS system using readily available and inexpensive circuit elements so that biomedical engineers from developing countries can maintain the instrumentation easily. In this research work, multi-frequency EIS system has been designed and to avoid complexity of the design of EIS the four electrode system is constructed using function generator, enhanced howland voltage to current converter, Instrumentation amplifier, EIS automatic switching using microcontroller (ATmega8) and Butterworth bandpass filter. Measurements on resistive, reactive and oval shaped phantoms give a resolution that would allow impedance changes reported in clinical studies (e.g., epithelial tissue characterization, abdominal fat thickness, early breast cancer screening) to be measured with our proposed simple, non-invasive EIS system.

Keywords: *Electrical Impedance Spectroscopy, Multi-frequency, Breast Cancer, Instrumentation*

I. INTRODUCTION

BREAST CANCER IS one of the most common cancers and the leading cause of cancer death among women worldwide [1] [2].Breast cancer incidence is increasing over the year with more than 1 million reported each year [3]. In addition to that an average 37,300 women died globally in conjunction to the disease [2][4].As there is no cancer registry system in Bangladesh, so we do not have accurate data on this. Like other developed countries definitely the number of patients is increasing day by day in Bangladesh. The most common form of screening system available to the mass people is mammography. Mammography is the process of using low dose x-ray to examine the human breast. Use of x-ray is always harmful for human body. Mammography is an expensive and health hazardous breast screening procedure .Electrical Impedance Spectroscopy (EIS) has been the subject of quite intensive research in breast cancer screening for about 20 years and yet to be established as a routine tool in health care. Electrical Impedance Spectroscopy (EIS) is a medical imaging technique in which an image

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of the conductivity or permittivity's of part of the body is inferred from surface electrical measurement. There are several advantages of EIS over other medical imaging techniques.

1. It is comparatively cheap technique over other imaging technique.
2. There are no known health hazards attached to it.
3. Data can be collected very rapidly so that change in function can be measured.
4. By making spectral measurement tissue characterization can be measured.
5. Long term monitoring physical function is possible.

Considering the advantages of the technique and the socio-economic condition of the poor people in Bangladesh, EIS could be a relief who do not have enough money for expensive medical imaging technique like Mammography and MRI.

Tissue Impedance Basics and relevance to cancer:

Electrical impedance is a term used to represent resistance offered by an object to current which has both frequency dependent and frequency independent element

When the measurements are made using AC signals of different frequencies these properties show up which may be utilized judiciously to identify the properties of particular tissue. Measurement of electrical impedance provides a means for characterization of tissue properties. The impedance **Z** is given by ohm's law, **I=V/Z**, where **I** is the electrical current passing through the object of interest and **V** is the potential drop across it. Certain cancer cells have frequency dependent impedance variation which is significantly different from that of normal cells. Hence electrical impedance or Bioimpedance measurement at different frequencies provides a means of diagnosis and monitoring of such cancerous organs. Human body is simplistically stated that a fluid having ions both positive and negative ions which are revolving.

Most often Biological tissue is composed by group of cells which are surrounded by cell membrane containing the intercellular fluid inside the cell membrane that are suspended on extracellular fluid. Both intercellular and extracellular fluid is rich in proteins and electrolytes. Such composition provides them ionic conductivity which is known as electrical conductivity. One of the important constituent in cell plasmatic membrane is known as cell membrane. The total structure formed by the intercellular fluid, plasma membrane and extracellular fluid forms a conductor-dielectric-conductor like structure behaving as a capacitor. A popular electrical equivalent circuit of human cell is proposed by K.S. Cole [5] and is given below Fig. 1.

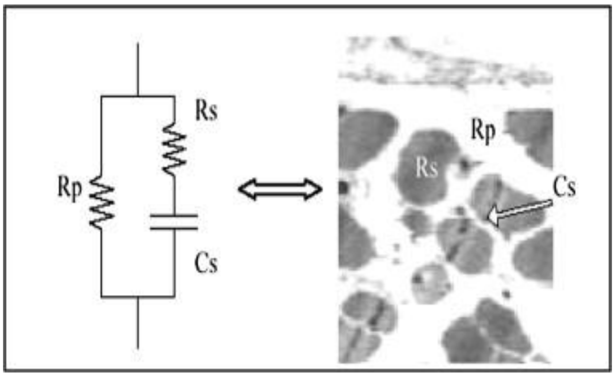


Fig. 1: A simplified Cole-Cole model for biological tissue

The equivalent circuit parameter may be approximately related to physical parameter as follows. The resistance of extracellular fluid is given by $\mathbf{R_p}$; **C** is the overall cellular capacitance of cellular membrane and $\mathbf{R_s}$ is the intercellular resistance. The equivalent circuit has both resistive and reactive components i.e. having frequency dependent and frequency independent term. The combination is said to be impedance or Bioimpedance as mentioned before. Again the cell membrane thickness and its electrical properties, the size of the cell, the size of nucleus inside, the packing density of the cell all of these will contribute to measured impedance and its variation with frequency. Such information has been used to characterize from breast of female with the aim of differentiating between the cancerous and noncancerous tissues. The bioimpedance variation of normal cell and cancerous cell is the key to diagnosis.

It is expected that there will change in bioimpedance between normal and cancerous tissue which is the base of Electrical Impedance Spectroscopy for early breast cancer screening. Relatively large variation of bioimpedance between normal tissue and cancerous tissue is mostly found in the frequency range of 1 KHz to 100 KHz and from 1 MHz to 10 MHz. Our proposed low cost, non-invasive EIS system works in the frequency range of 1 KHz to 100 KHz as the high frequency ICs are not available in the local market of Bangladesh. This paper presents the design of instrumentation for a multi-frequency four electrode EIS system constructed using low cost IC chips commonly available in Bangladesh.

II. MATERIALSAND METHODS

1) Specifications:

The design requirements which are based on the published variation of tissue impedance with frequency [6][7][8][9] includeed.10 measurements frequencies in the range of10 KHz to 100 KHz; a complete set of multi-frequency measurements are made using four electrodes and to only use electronic component could be sourced locally within Bangladesh. The specification of multi-frequency EIS system described in this paper is given below:

Features	Specifications
Excitation Frequency	10-100 KHz
Drive current	1 mA(p-p)
Current Drive output impedance	>50 kΩ

Table 1: Specification for multi-frequency EIS system

The design block diagram shows in Fig.2 describes the system operation and design methods.

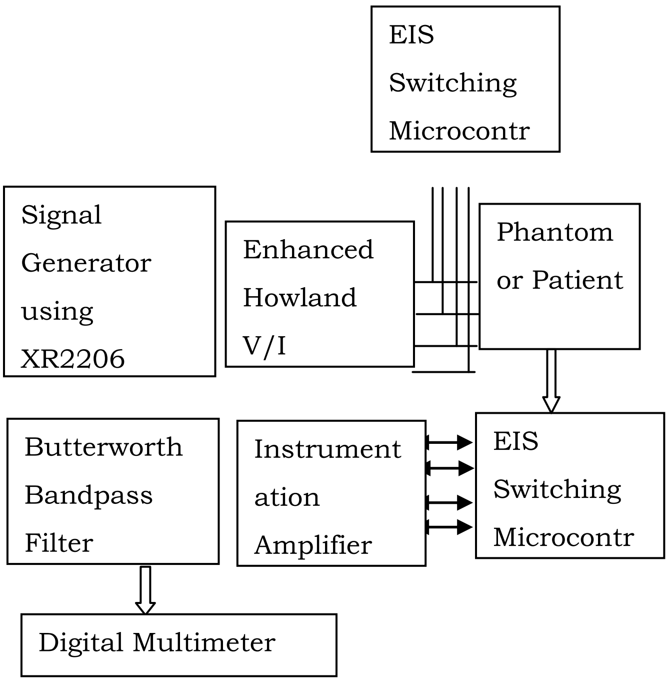


Fig.2: Block Diagram of the designed Multi-frequency EIS System

The Signal generated of various frequencies controlled externally. The voltage-to-current converter converts the voltage signal to low amplitude constant current signal.The current is pushed through two separate electrodes and injected to the organ under test and the response is collected through two other electrodes. When current is injected between 1, 2 electrode and then voltage is measured in 3, 4 electrodes and the sequence is repeated by switching to complete one profile of bioimpedance data. A program is designed and implemented for automatic switching between the electrodes have been done using microcontroller (ATmega8).The recipient electrodes feed the signal to a wide band, high gain, high CMRR instrumentation amplifier. To improve signal-to-noise ratio, the signal then feeds to a wide bandwidth bandpass filter and finally the RMS voltage is measured using Digital Multimeter.

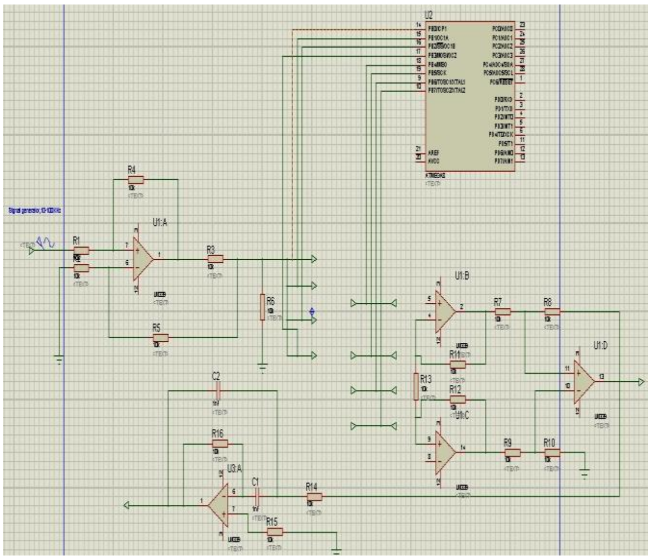


Fig.3: Schematic Diagram of Full System

Current Drive Section:

In tetraploar EIS measurement an alternating current of constant amplitude is injected into the body through two electrodes and the resulting voltage across two other electrodes is measured. To maintain the amplitude of the applied current constant, a current source with high output impedance is required. The current drive section is designed by cascaded Function generator using XR-2206 IC and Enhanced Howland V/I converter.XR-2206 IC is a monolithic function generator which is locally available IC in Bangladesh. By varying the value of resistors and capacitors different frequencies signals can be generated .The generated signal has excellent temperature stability, wide sweep range and adjustable amplitude. The output amplitude can be adjusted externally by varying the resistor value of **R_3**.

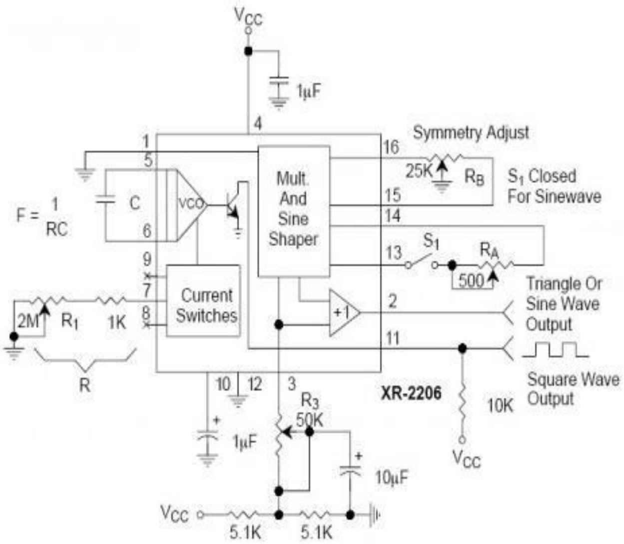


Fig.4: Working Circuit Diagram of sine wave generation with minimum harmonic distortion.

Enhanced howland V/I converter:

High frequency low level current is to be injected to the human body which needs a constant current source as bioimpedance varies on diseased condition as well as one person to another.V/I converter or constant current source is an essential part of the multi-frequency EIS system. The performance of V/I converter is therefore critical. The structure of the enhanced howland circuit is very simple and its performance is predictable [10][11].

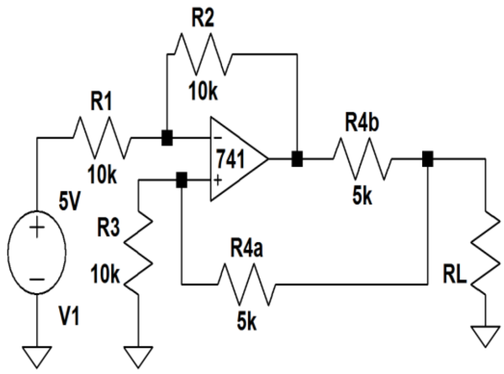


Fig. 5: Enhanced Howland Voltage-to-current converters

EIS automatic switching:

The four electrode EIS needed two tetraploar measurements for each frequency where the direction of current drive and voltage measuring electrode pairs were altered [12].The two electrodes will be selected in rotating manner for current injection like 1,2;2,3;3,4;4,1 and similarly for voltage measurement the rotation of selection should be just opposite 4,1;3,4;2,3;1,2.

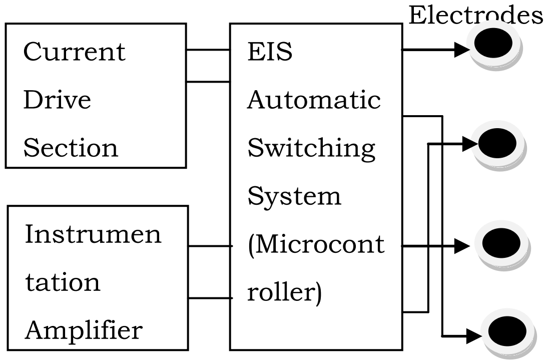


Fig.6: EIS automatic switching system when current is injected through 4, 1 electrodes and voltage is measured 2, 3 electrodes.

The selection is done by using AVR ATmega8 microcontroller. In this research work we have used Arduino board consists of 5V linear regulator and 16 MHz crystal oscillator. All boards are programmed over RS-232 serial connection.

Instrumentation Amplifier:

An instrumentation amplifier with voltage gain of 50 and CMRR of 63 dB at 10 KHz and 37 dB at 1024 KHz has been used. A high bandwidth op-amp LM339 IC has been used which is available at local market of Bangladesh. The instrumentation amplifier circuit in Fig.7 is used to monitor the voltage output from two voltage monitoring electrodes connected to the human body.

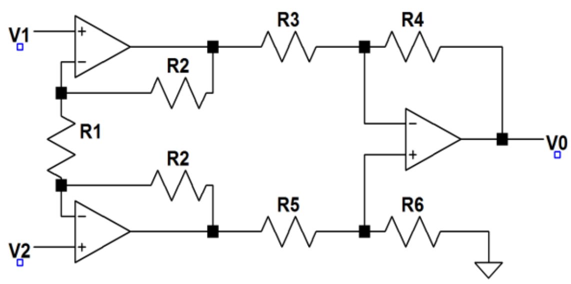


Fig.7: An instrumentation amplifier using LM339 IC

Butterworth Bandpass Filter:

To improve signal-to-noise ration bandpass filter has been designed and implemented.

The frequency range of consideration is 5 KHz to 100 KHz in our proposed EIS system. The bandwidth is chosen 100 KHz. A high frequency LM339 op-amp has been used for the bandpass filter design.

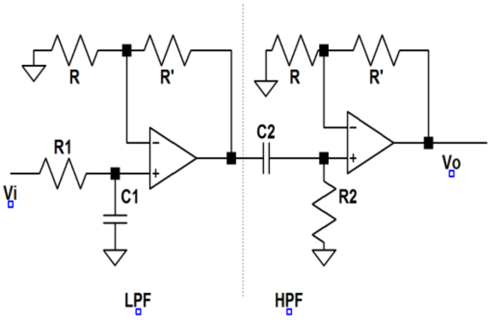


Fig.8: A Butterworth Bandpass filter

This section should provide the reader with all the information necessary to repeat the work. For a modification of published methodology, only the modification needs to be described, with reference to the original source. Statistical analysis of the data (where applicable) is mandatory, using appropriate methods, which must be cited.

III. RESULTS

As there is no permission from Bangladesh Medical Research Council, so bioimpedance data could not be collected from real breast tumour patients. In addition to that electrical current injection method is new to doctor and patients in Bangladesh. To test the accuracy and reproducibility of the measurement system, current was injected through various known resistor chains and the corresponding impedance was measured at each frequency. Each measurement was repeated ten times to study the measurements reproducibility.

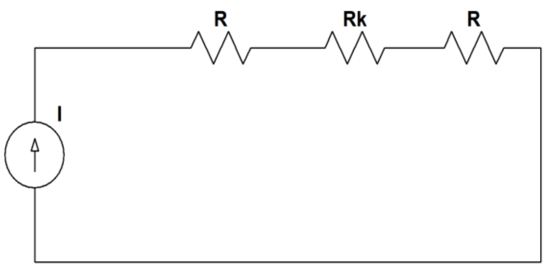


Fig.9: Resistive Phantoms used to study the accuracy of the designed EIS system

The resistor **R**in Fig.9 was set to 1 KΩ to simulate the electrode-tissue contact impedance. If the applied known resistance was $\mathbf{R_{known}}$ ($\mathbf{R_k}$ in Fig.9) and the resistance measured by multi-frequency EIS system was $\mathbf{R_{measured}}$ then the percentage of error was calculated using equation(1)

$$Error = \frac{Rknown - Rmeasured}{Rknown} \times 100\% \text{---} \ (1)$$

Fig.10 shows the percentage of error in the measured resistance values against actual resistance values at three different frequencies. The measurement error was well below 2.2%.

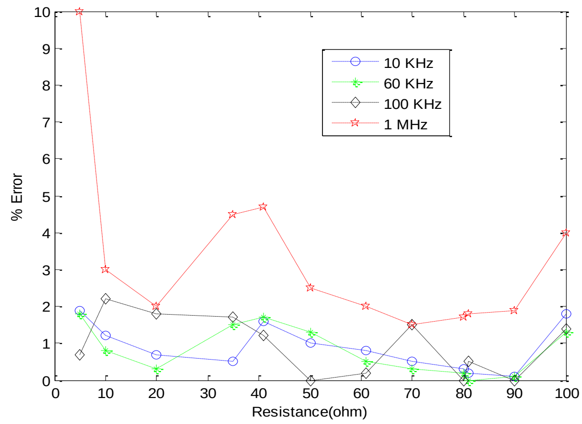


Fig.10: Percentage of measurement error at four different frequencies.

The designed EIS system was also tested for capacitive loads by replacing the load resistor $\mathbf{R_{known}}$(Fig.9) with a Cole-Cole model Phantom (74Ω in parallel with 24Ω in series with 4.7 nF) Fig.11 shows the Cole-Cole phantom and Fig. 12 shows the measured impedance value against calculated impedance value for this phantom and the maximum error is 2 %.

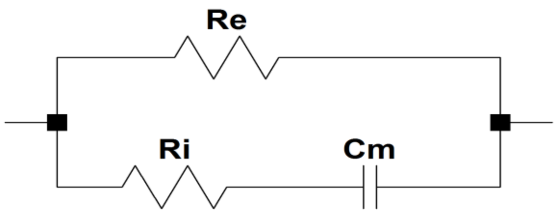


Fig.11: Capacitive Cole-Cole Phantom

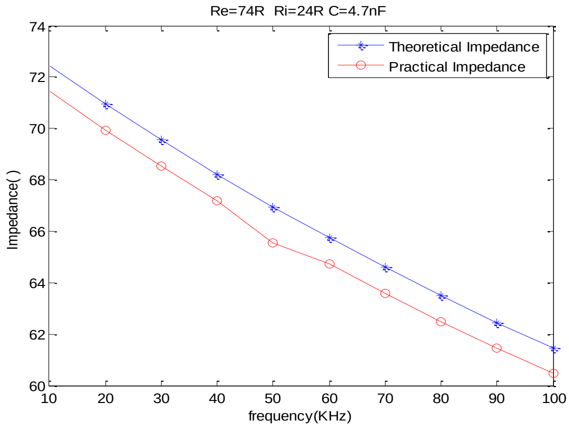
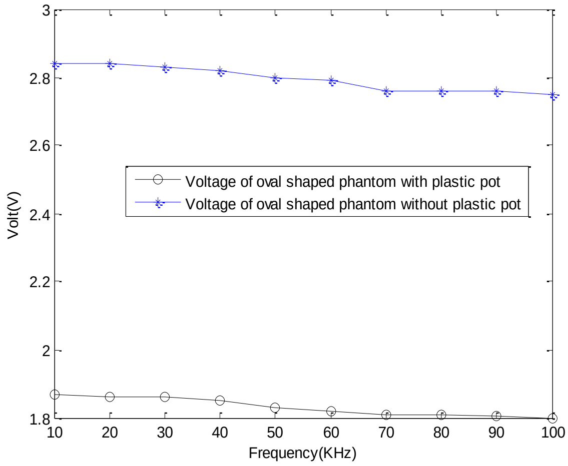


Fig.12: Comparison between measured impedance and calculated impedance of a Cole-Cole Phantom

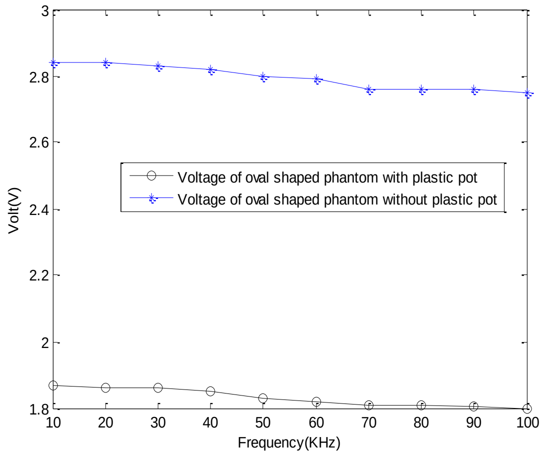
An oval shaped Plastic phantom has been built with a height of 4 inches and its internal shape is hollow with 16 inches perimeter; so that saline water can be entered into it. Three layers of plastic phantom are used for measuring impedances.

Fig. 13: An oval shaped Plastic Phantom

The perimeters of the first, second and third layers are respectively 16, 14 and 12 inches. Four screws with wires are used as electrodes and all electrodes are equally spaced. The layer wise phantom studies are done and the measured curves are given below. A plastic pot with 3 inches is also used for measuring impedances. When it is inserted in the oval shaped phantom then variation of impedances is also detected.

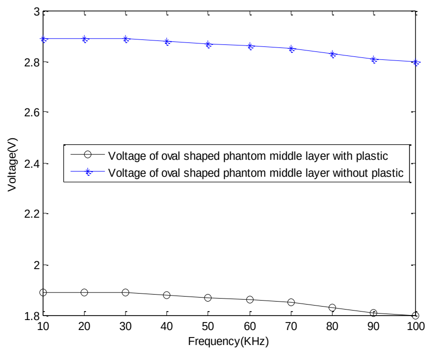


(a)

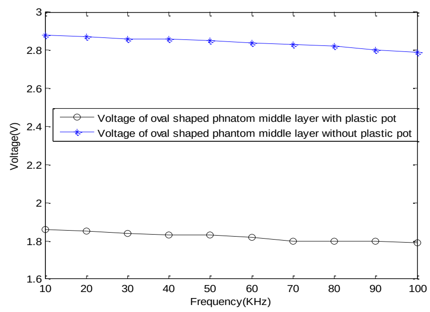


(b)

Fig 14: Voltage vs. frequency curve of lower layer oval shaped phantom (a) when current is injected between 1, 2 electrodes and voltage is measured between 3,4 electrodes alternately.(b) When current is injected between 2,3 electrodes and voltage is measured between 4,1 electrodes alternately.

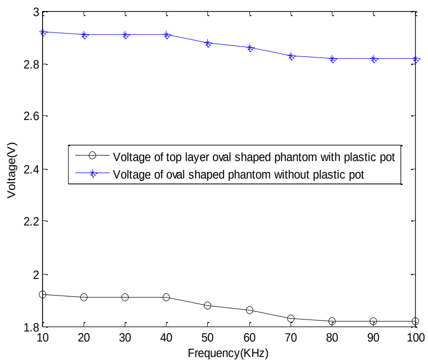


(a)



(b)

Fig.15:Voltage vs. frequency curve of middle layer oval shaped phantom (a) when current is injected between 1,2 electrodes and voltage is measured between 3,4 electrodes and alternately (b) When current is injected between 2,3 electrodes and voltage is measured between 4,1 electrode and alternately.



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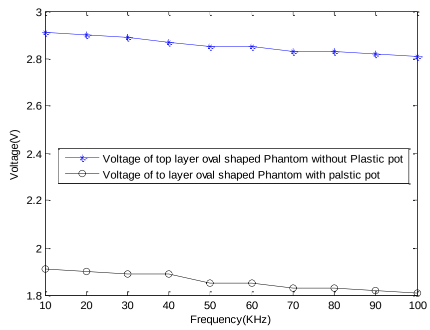
(a)



(b)

Fig. 16: Voltage vs. Frequency curve of top layer oval shaped phantom (a)when current is injected between 1,2 electrodes and voltage is measured between 3,4 electrodes and alternately.(b)When current is injected between 2,3 electrodes and voltage is measured between 4,1 electrodes and alternately.

From the above three layer curves, it is very much clear that the impedance of a phantom for a particular layer is quite constant. As there is no capacitive effect of a phantom so variation of impedances between with frequencies should be less. Theoretically the impedance should remain constant for a particular object and for a particular layer. Our designed EIS system measured impedance variation is less and the percentage of error is always less than 3.3%.The curves are very much similar when current and voltage injection occurs in an alternating manner for electrodes that means the designed EIS system follows the reciprocity theorem.

For measuring sensitivity and detecting capability of our designed EIS system, we have used a 3 inch rectangular plastic pot and the variation of impedances is quite easily observable.

Therefore, the performance of the measurement device described in this research work is adequate to undertake field trials to the breast cancer patients.

IV. Conclusion

Multi-frequency Electrical Impedance Spectroscopy (EIS) has been designed and implemented considering the socio-economic condition of the developing countries like Bangladesh. The system has been designed using local available low-cost ICs. As there is no permission from Bangladesh medical research council, so we could not take any practical data of breast cancer patients. Measurements on resistive, reactive and oval shaped phantom gives a resolution that the proposed low cost, non-invasive EIS system is adequate to undertake field trials in breast cancer screening for early detection.

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