2014 CMBEC37 Conference
Vancouver, BC
May 21 – 23, 2014

# COMBINING TWO BREAST CANCER DIAGNOSIS TECHNOLOGIES: DIFFUSE OPTICAL TOMOGRAPHY WITH EIS

Majid Shokoufi, Parvind Grewal, and Farid Golnaraghi*
Mechatronic Systems Engineering, School of Engineering Science, Simon Fraser University
250-13450 102 Avenue, Surrey, BC, Canada V3T0A3
*E-mail any correspondence to: mfgolnar@sfu.ca*

## ABSTRACT

Both Frequency-Domain Diffuse Optical Tomography (FD-DOT) and Electrical Impedance Spectroscopy (EIS) are mature and developed technologies that have been used separately for breast cancer detection. In this paper we have developed and present a handheld diffuse optical tomography probe combined with EIS to monitor, non-invasively, real time biological tissue activity *in vivo*. The proposed probe has two near-infrared wavelengths LEDS (capsulated in one package) and one photodiode, and two Ag/AgCl electrodes. Using FD-DOT with multispectral evaluation algorithm, we can measure Tissue Oxygenate Index (TOI), change of TOI, Tissue Oxygenate Hemoglobin (TOH) and Tissue Deoxygenate Hemoglobin (TDH) as well as determine the concentrations of water, lipids and optical scattering properties in normal and cancerous breast tissue. The EIS provides information regarding electrical properties of tissue specifically increased cellular water, sodium content, altered membrane permeability, and changed packing density and orientation of cells. The two point EIS is capable of a frequency sweep from 1 Hz to 50 MHz, but to overcome skin impedance and electrode polarization issues, the 100KHZ to 1MHZ frequency range has been considered for the present study. The combined FDOT-EIS system is used to provide simultaneous electrical as well as optical characteristics of *in-vivo* tissue.

## INTRODUCTION

Breast cancer is an uncontrolled growth of breast cells and is the second leading cause of cancer related death in women; moreover it remains the first leading cause of cancer-related death in women under the age of 40 in North America. In 2013, it was expected to diagnose about 23,800 women and 200 men with breast cancer in Canada, and 232,340 women and 2,240 men with breast cancer in USA. It was also anticipated that 5000 women and 60 men in Canada, and 39,620 women and 410 men would die from breast cancer in 2013 in Canada and USA, respectively [1], [2]. Mammography, ultrasound and magnetic resonance imaging (MRI) are popular technologies being used in breast imaging for diagnosing breast cancer. The primary screening method has been X-ray mammography[3], which is currently the golden standard for breast cancer screening [4]. Though mammography is a very useful and promising technique but it is only advised for women between the age of 50 and 74 years of age[5], due to a high false negative detection ratio for younger women [4]. Using ionizing radiation (X-ray) also poses a serious health risk to women as it can even increase the chance for cancer development [6], [7]. Limitation of mammography have motivated researchers to develop alternative breast cancer detection system such as Magnetic Resonance Imaging (MRI), Ultrasound (US), Electrical Impedance Tomography (EIT), Diffuse Optical Tomography (DOT), Elastography and so forth[4]. In order to improve accuracy, sensitivity, specificity and positive predictive value, combination of different detection technique are of interest to researchers as well. The objective of this paper is to design, implement and demonstrate the concept of using DOT and EIS modality simultaneously to measure optical and electrical properties of breast tissue *in vivo,* in order to diagnosis malignant from benign tissue. One of the main advantages of this technique is that, using these two modalities gives more information about the tissue and both are non-invasive.

## THEORETICAL DEVELOPMENT

### A. Optical properties of biological tissue

Light interaction with Biological tissues have characterized by optical scattering and absorption properties of tissue. Optical absorption of biological tissue is weak in the wavelength range of 550nm to 1350nm which is associated with the fact that living tissues do not contain strong intrinsic chromophores that would absorb radiation within this spectral range. Mean free path of photons in this wavelength range is very small (in the order of 100μm) whereas the absorption length (mean path length before photon absorbed) is in the order of centimeter[8]. Long absorption length in the biological tissue such as brain, breast and etc. allow to measure optical properties of tissue *in vivo*. Absorption spectra of four primary optical absorbers in the breast has been shown in fig. 1: oxy-hemoglobin ($HbO_2$) and deoxy-hemoglobin (Hb), fat, and water [9]. It illustrates why the near-infrared (NIR) wavelength window from 650-900 nm is ideal for tomographic imaging of tissue. At the lower visible wavelengths the absorption of $HbO_2$, fat and water are significantly lower than Hb, but the absorption of water and fat is still quite low in NIR window (it increases dramatically above 1000 nm)[10].

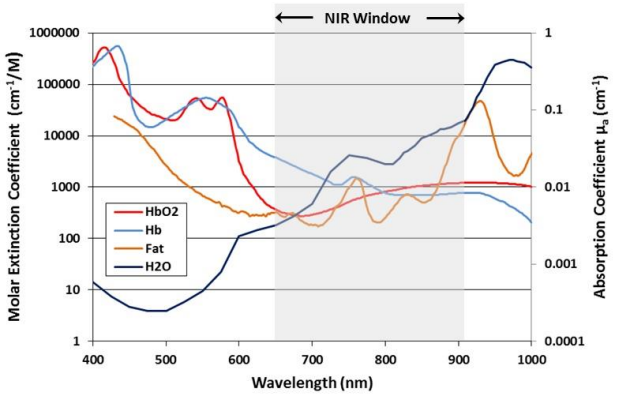


Figure 1: Optical absorption of oxy-hemoglobin ($HbO_2$), deoxy-hemoglobin (Hb), water ($H_2O$), and fat plotted versus wavelength.[11]

### B. Electrical impedance properties of biological tissue

Tissue impedance has been commonly modeled as parallel RC circuit (Fig.2). $R_1$ depicts the extracellular resistance, $R_2$ the intracellular conduction and C the membrane capacitance.

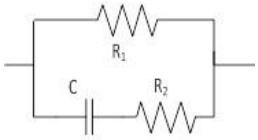


Figure 2: Three Element RC Model

A popular methodology of depicting tissue impedance is through Cole plots, based upon work of Cole and Cole [12], using measurements performed in frequency domain. Furthermore, multi-frequency measurements have been used to classify malignant tissue with promising results[13]. EIS based upon Cole equation [12] is useful to monitor the intra/extra-cellular volume imbalances or the inter-cellular junctions resistances and detect tissue structural alterations by analyzing the central frequency, resistivity at low frequencies and $\alpha$ parameter in the ($\alpha$, $\beta$) dispersion regions [14]. The EIS method is capable of characterizing and classifying tissue by extracting tissue specific parameters from the frequency spectrums[15]. These parameters help determine the intracellular and extracellular properties of the cells. Tissue properties are not only dependent upon the extracellular medium (ionic in nature) and intracellular medium, but also on the cell structure that is capacitive in nature and consists of semi-permeable membranes through which the ions move in and out.

## DEVELOPMENT OF EXPERIMENTAL SYSTEM

An LED with two near-infrared wavelengths of light (760nm and 940nm) and two Ag/AgCl electrodes have been used to measure optical and electrical properties of tissue. The light passes through the sample and is absorbed and scattered as it travels to a photodiode detector configured in reflectance geometry located 3 cm away from the sources and two EIS electrodes are located 3 cm away each other as shown in fig. 3. The input light is generated by

multi-wavelength LED capsulated in one package made by Epitex Company. Table 1 shows specification of the light source.

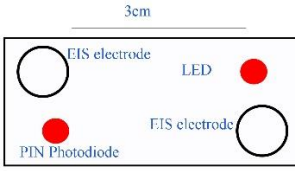


Figure 3: Light Source, detector and EIS electrode layout.

Table 1: Optical characteristics of light source at 25°C made by Epitex Company.

| item | | sym | current | Typ | ut |
|---|---|---|---|---|---|
| radiant power | 760nm | Po | IF=50mA | 15 | mW |
| | 940nm | | | 14 | mW |
| Peak $\lambda$ | 760nm | $\lambda$p | IF=50mA | 760nm | |
| | 940nm | | | 940nm | |
| Half width | 760nm | $\Delta\lambda$ | IF=50mA | 30 | nm |
| | 940nm | | | 50 | nm |

A dynamic electrical impedance spectroscope (model: HF2IS) from Zurich Instrument has been used as a signal processor to drive light source and EIS electrode, and gather signals from photodiode detector and EIS electrode. As illustrated in fig. 4. The instrument has two outputs with capability of four frequency mixer. Output2 has been used to produce required signal for LEDs. Two sinusoidal wave, 10KHz and 14Khz, have been applied to 760nm and 940nm LEDs, respectively. These frequencies separated by an external band pass filter, as shown in fig. 4, and drive the LEDs. Photodiode detector (VISHAY PIN Photodiode- BPV10) is connected to input2 on HF2IS via programmable current amplifier HF2TA. Current gain of this amplifier and drivers' current of LEDs is defined automatically by the amount of photons that come through the photodiode. Output1 and input1 have been used for two point electrical impedance spectroscopy. Output1 is connected directly to one of the electrode and second electrode is connected via programmable current amplifier (HF2TA). The Impedance Spectroscope has ability to sweep frequency from DC to 50 MHz, but to overcome skin impedance and electrode polarization issues, the 10KHZ to 1MHZ frequency range has been considered for the present study.

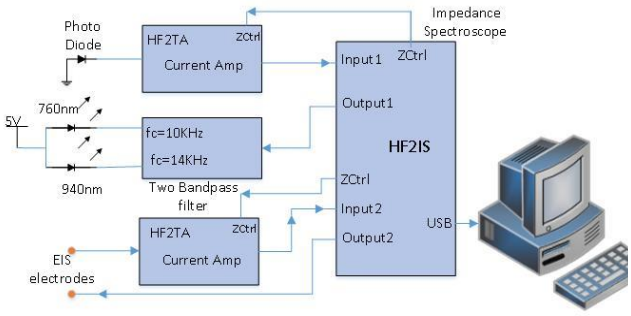


Figure 4: Schematic diagram of the system

## EXPERIMENTAL RESULTS

Fig.5 shows Fourier Transform of back reflected light from forearm tissue and reference surface. As expected the absorption of 940nm light is much higher than 760nm. Using FD-DOT technique, the optical signal can be extracted from very noisy signal. Multi-frequency EIS over the forearm at 50 different frequencies is depicted in Fig.6. The Nyquist plot is used to represent tissue admittance. The real admittance (X-axis) is plotted against the imaginary admittance (Y-axis) as tissue admittance is complex in nature. Usually, the negative Y-axis is considered for better representation. The frequencies increase from left to right.

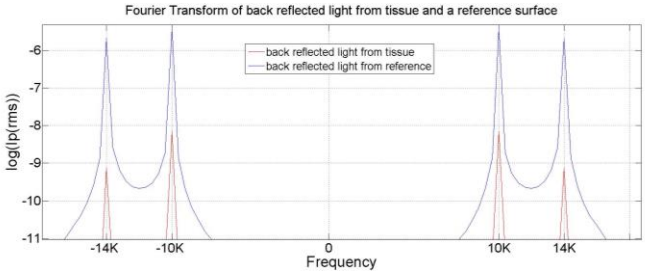


Figure 5. Fourier Transform of back reflected light from forearm tissue and reference surface

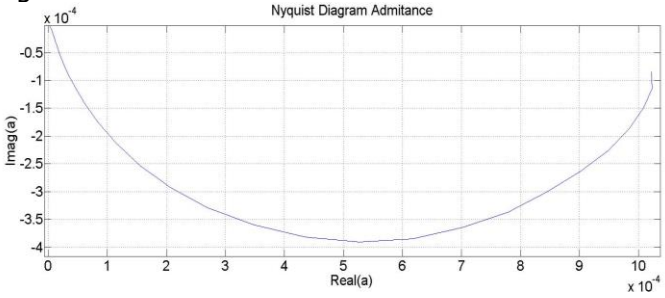


Figure 6. Nyquist plot of real admittance against the imaginary admittance

The designed probe can simultaneously measure optical and electrical properties of

biological tissue. This device and accompanying software will facilitate future clinical studies exploring the optical and electrical impedance signatures of anomaly regions in the breast, but it is not limited to breast imaging. Indeed, it can be used for static and dynamic measurements on many other tissues, for example, the brain or limbs. Also it can be used for many existing clinical optical and electrical impedance studies by providing real-time measurements.

## CONCLUSION

In this paper, we have presented, designed and developed a combined technique for breast cancer diagnosis probe which uses diffuse optical tomography (DOT) and electrical impedance spectroscopy (EIS), simultaneously. DOT and EIS measure tissue oxygenation level and electrical cellular properties, respectively. The EIS system measures impedance of the tissue for full spectrum range from 10KHz to 1 Mhz. DOT can gather data at 10Hz, which is appropriate for dynamic measurement of optical properties of tissue underneath of the probe. Although, the speed of the hardware and software are suitable for real time measurement but the speed could be increased by using optimized software. Sensitivity, accuracy and specificity of the test will increase with measuring optical and electrical properties of tissue, simultaneously. The authors are looking forward to work to use multi wavelength light source (more than two) to increase accuracy of the measurement.

## ACKNOWLEDGEMENTS

Financial support of this project was provided in-part by the Natural Sciences and Engineering Council of Canada (NSERC).

## REFERENCES

[1] R. Siegel, D. Naishadham, and A. Jemal, "Cancer Statistics , 2013," *A Cancer J. Clin.*, vol. 63, no. 1, pp. 11–30, 2013.

[2] "Canadian Cancer Statistics 2013," Toronto, 2013.

[3] L. Tabár and P. B. Dean, "A new era in the diagnosis and treatment of breast cancer.," *Breast J.*, vol. 16 Suppl 1, pp. S2–4, 2010.

[4] A. M. Hassan, S. Member, M. El-shenawee, and S. Member, "Review of Electromagnetic Techniques for Breast Cancer Detection," *IEEE Rev. Biomed. Eng.*, vol. 4, pp. 103–118, 2011.

[5] H. D. Nelson, K. Tyne, A. Naik, C. Bougatsos, B. K. Chan, and L. Humphrey, "Screening for Breast Cancer: Systematic Evidence Review Update for the U. S. Preventive Services Task Force," *Ann Intern Med*, vol. 151, no. 10, pp. 716–726, 2009.

[6] A. Berrington de González and S. Darby, "Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries.," *Lancet*, vol. 363, no. 9406, pp. 345–51, Jan. 2004.

[7] C. M. Ronckers, C. a Erdmann, and C. E. Land, "Radiation and breast cancer: a review of current evidence.," *Breast Cancer Res.*, vol. 7, no. 1, pp. 21–32, Jan. 2005.

[8] S. L. Jacques and B. W. Pogue, "Tutorial on diffuse light transport.," *J. Biomed. Opt.*, vol. 13, no. 4, p. 041302, 2008.

[9] S. van de Ven, S. Elias, A. Wiethoff, M. van der Voort, A. Leproux, T. Nielsen, B. Brendel, L. Bakker, M. van der Mark, W. Mali, and P. Luijten, "Diffuse optical tomography of the breast: initial validation in benign cysts.," *Mol. Imaging Biol.*, vol. 11, no. 2, pp. 64–70, 2009.

[10] S. A. Prahl, "Optical properties spectra," *S. A. Prahl,*. [Online]. Available: http://omlc.ogi.edu/spectra. [Accessed: 01-Sep-2013].

[11] M. Flexman, "Dynamic Digital Optical Tomography for Cancer Imaging and Therapy Monitoring," COLUMBIA UNIVERSITY, 2012.

[12] K. . Cole and R. . Cole, "Dispersion and absorption in dielectrics," *J. Chem. Phys.*, vol. 9, pp. 341–351, 1941.

[13] R. Liu, X. Dong, F. Fu, F. You, X. Shi, Z. Ji, and K. Wang, "Multi-frequency parameter mapping of electrical impedance scanning using two kinds of circuit model.," *Physiol. Meas.*, vol. 28, no. 7, pp. S85–100, Jul. 2007.

[14] A. Ivorra, M. Genescà, A. Sola, L. Palacios, R. Villa, J. Aguiló, and G. Hotter, "Bioimpedance dispersion width as a parameter to monitor living tissues," *Physiol. Meas.*, vol. 26, no. 2, p. S165, 2005.

[15] T. E. Kerner, K. D. Paulsen, A. Hartov, S. K. Soho, and S. P. Poplack, "Electrical impedance spectroscopy of the breast: clinical imaging results in 26 subjects.," *IEEE Trans. Med. Imaging*, vol. 21, no. 6, pp. 638–45, Jun. 2002.