Compression-dependency of soft tissue bioimpedance for *in-vivo* and *in-vitro* tissue testing

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Abstract

The present study determines the effect of compression over bioimpedance of healthy soft tissue (*in-vitro* and *in-vivo*). Electrical impedance spectroscopy (EIS) is a promising tissue characterization and tumor detection technique that uses tissue impedance or admittance to characterize tissue and identify tissue properties as well as cell structure. Variation in EIS measurements while applying pressure suggests that compression tends to affect soft tissue bioimpedance. Moreover, the displacements in tissue caused by applied compression may provide useful information about the structure and state of the tissue. Thus combining the changes to the electrical properties of tissue resulted by applied compression, with the changes in tissue displacements caused by applied compression, and consequently measuring the effect that electrical and mechanical properties have on each other, can be useful to identify tissue structure. In this study, multifrequency bioimpedance measurements were performed on *in-vitro* and *in-vivo* soft tissue at different pressure levels. Increasing compression on the *in-vitro* tissue results in an increase in both extracellular resistance and membrane capacitance while it causes a reduction in the intracellular resistance. However, as the compression over the *in-vivo* samples increases, the intracellular and extracellular resistance increase and the membrane capacitance decreases. The *in-vivo* measurements on human body are also tested on contra-lateral tissue sites and similar tissue impedance variation trends are observed in the contra-lateral sites of human body. The evidence from these tests suggests the possibility of using this EIS-Pressure combined measurement method to improve tumor detection in soft tissue. Based upon the observations, the authors envision developing an advanced model based upon the Cole model, which is dependent on tissue displacements.

Keywords: Bioimpedance, soft tissue, compression, *in-vivo*, *in-vitro*, electrical impedance spectroscopy

Introduction

Electrical and mechanical properties of tissue play a prominent role in tumor detection [1–4]. Much research has been performed independently on the mechanical and electrical properties of soft tissue and the effect that tissue pathology has on these properties. However, the link between mechanical and electrical properties of tissue and their correlation to pathological fluctuations remains unclear.

Pathology in soft tissue changes the stiffness of its local area [5]. Stiffness of soft tissue, which differs in tumor and its surrounding healthy tissue, can be estimated by

measuring the applied external load to the body surface and its resultant displacement [6]. In the majority of breast examinations, palpation method is used to examine the breast [7], thus characterizing the compressive behavior of soft tissue provides insight into the mechanism of tissue pathology. Fischer introduced a device to quantify palpation of tissue in an objective manner [9]. He suggested the use of a tissue compliance meter in order to monitor the variation in the soft tissue modulus of elasticity when there is a malignancy in the tissue. Fung *et al* [8] identified the effect of pathological fluctuations on the elastic characteristics of the microscopic and macroscopic structural organization of tissue. Although these methods provide useful insight regarding the elastic features of tissue, some researchers looked into measuring the modulus elasticity of the tissue by means of imaging techniques. Many techniques have been proposed for examining abnormal breast tissue based on imaging the elastic contrast [10, 11]. Most imaging techniques record the images of the tissue at two different applied forces and then the displacement of tissue is measured. Given the applied force and the displacement of soft tissue, its stiffness can be computed.

Soft tissue behavior is mostly close to the behavior of viscoelastic materials. However, in order to develop a mathematical model for behavior of soft tissue using a single elastic or shear modulus, most researchers have assumed that soft tissue is isotropic, elastic [12–15] and nearly incompressible [16]. Under these assumptions, Sarvazyan *et al* reported a study of 150 specimens of normal and cancerous tissues which showed that cancerous tissue can be as much as 7 times stiffer than normal tissue [14].

Besides, Fricke and Morse observed a higher capacitance in breast malignant tumors in comparison with the healthy breast [17]. Later in 1990, Morimoto *et al* studied the electrical impedance of breast tumors *in-vivo* and calculated the intracellular resistance, the extracellular resistance and cell membrane capacitance of normal and pathological tissue based on the impedance spectra at a frequency range of 0 to 300 kHz and a circuit model [18]. They reported a statistically significant increase in the intra- and extracellular resistances and a statistically significant decrease in the membrane capacitance in the pathological tissue. Jossinet *et al* performed an experiment on 64

subjects with normal, benign and carcinoma breast tissues [19]. Jossinet compared the complex impedance loci of normal and carcinoma in a frequency range of 488 Hz to 1 MHz and an obvious difference was observed in the shape and location of the loci at frequencies above 125 kHz for normal, benign and carcinoma tissue. Keshtkar *et al* performed electrical impedance measurements on 38 *in-vivo* benign and malignant subjects at a frequency range of 2- 348 kHz [20]. The results revealed that the impeditivity of malignant subjects were significantly higher than the impeditivity of benign subjects which was in contrast to the results presented by Brown *et al* [21] and Gonzales-Correa [22].

Kim *et al* [23] developed a new analysis technique on the admittance of freshly-excised malignant breast tissue and its surrounding normal tissues which resulted in a clear distinction between the pathological and normal tissues. In a study conducted by Laufer *et al* [17], the Cole model, which is an electrical circuit equivalent model consisting of one resistor in parallel with a resistor and a constant phase element (CPE) which are in series [24], was fitted to the impedance data. The four parameters of the Cole model were compared in the cancerous and normal liver tissue. Obtaining the parameters of the Cole model gave a better understanding of the tissue in cellular level. The results illustrated that the conductivity of cancerous tissue was much higher than that of normal tissue.

Although many studies have focused on electrical and mechanical properties of healthy and cancerous tissue, the correlation of electrical and mechanical properties in healthy and cancerous tissue has not been established and compared yet.

Soft tissue electrical properties change due to tissue compression [25]. Different types of tissue have diverse compressive behaviors. Little within the literature has been published regarding the effect of compressive behavior of soft tissue on the changes of electrical properties. Gonzalez *et al* [26] measured the resistivity of the squamous and columnar tissues of three rats. The bioimpedance of these samples were measured under the applied pressure. They observed that by increasing the applied pressure not only the resistivity increases, but also the difference in the changes of resistivity of two types of tissue was sizeable. They suggest that the different resistivity of each type of tissue can be an indicator of its structure. Belmont's test [27] on a soft tissue-mimicking phantom showed a decrease in the admittance of the phantom under compression. They showed that *tofu* can be used as a suitable phantom for bioimpedance measurements under applied pressure. They established a correlation between the viscoelastic behavior of *tofu* and its electrical admittance. It was illustrated in this study that the impedance is influenced by the amount of conductive fluid within a porous material.

Jossinet *et al* examined the impedance changes in tissue exposed to high-energy ultrasound and observed a 20% increase in impedance magnitude at low frequency and a 30% decrease in impedance magnitude at high frequency

[28]. Dodde *et al* [25] studied the electrical properties of tissue under compression at the cellular level. A non-linear behavior was reported by Dodde at a compression level around 60%. The findings of Dodde *et al* are discussed and compared to the results of this study in the discussion.

The purpose of the present study is to find the correlation between variations of tissue electrical properties with changes of displacements of soft tissue. We postulate that electrical properties of tissue are related to the mechanical properties and also any type of tissue has a specific electrical-mechanical properties based model. Since tumors in soft tissues change both the electrical and mechanical properties of tissue, it is postulated that healthy and tumorous tissues have different electrical-mechanical correlation. Thus, by finding this relationship and model, the structure, type and abnormality of the tissue can be estimated. Therefore, presence of inhomogeneity in the soft tissue electrical-mechanical behavior may help develop a tumor detection technique.

To test the validity of this claim, various types of *in-vivo* and *in-vitro* tissues are mechanically and electrically tested. As compared by [29], one model which fits to the measured data well is the Cole model [30, 31]. The modulus of elasticity of the tested tissues is calculated from the linear relationship of engineering stress-strain graphs. The effect that compression has on the electrical properties of tissue and also the relationship between electrical features and tissue displacement is elaborated in this paper.

Materials and methods

In this study, the bioimpedance and elastic modulus of twenty *in-vitro* chicken breast samples, two *in-vitro* rat breast samples and eleven *in-vivo* human subjects were measured. Ethics approval from the Office of Research Ethics, Simon Fraser University, was taken for collecting electrical and mechanical data of *in-vivo* human tissue. An advance approval of the animal care protocol was also obtained from the University Animal Care Committee of Simon Fraser University for *in-vitro* experiments. Details of the experimental setups, procedures and methods are given below.

Experimental setup and procedure

Bioimpedance and modulus of elasticity of *in-vivo* and *in-vitro* tissue were measured during electrical and mechanical experimental procedures by two different setups, which will be explained in the following sections.

Electrical impedance setup and procedure. Bioimpedance measurements of various types of tissue were conducted while incremental pressure levels were applied to the *in-vivo* and *in-vitro* tissue. For this experiment an impedance spectroscopy HF2IS along with a transimpedance amplifier HF2TA (TA) by Zurich Instrument (Zurich Instrument Inc., Switzerland) were interfaced. The detailed electrical

impedance system setup is explained by Grewal [32]. The bioimpedance measurements were conducted using a two point measurement technique [33, 34] at 50 frequencies in the frequency range of 5 kHz to 1 MHz under incremental compression levels. A one-finger wearable force sensor FingerTPS by Pressure Profile Systems (Pressure Profile Systems Inc., LA, USA) was worn over the examiner's index finger. Before performing the test, the force sensor was calibrated using a load sensor and the customized software "Chameleon TVR", available with the PPS sensors. The constant pressure was applied to the electrical electrodes located over the tissue by the examiner placing her index finger over the electrodes and applying constant pressure. The applied pressure was approximately held constant within 5% bound by the examiner monitoring the pressure value from the Chameleon TVR software. This procedure was repeated at six force levels (2.2–13.3 N) for chicken and rat samples and at 3 force levels (2.5–7.5 N) for human subjects.

In the *in-vitro* experiment, two samples were excised from each chicken breast and one sample was excised from each rat breast. Therefore, twenty chicken samples excised from ten chicken breasts and two rat samples excised from two rat breasts were chosen for the experiments. Samples were cut in a cuboid form using a sharp cutter from the same parts of the animals' breast to assure consistency in results. The samples were 4 cm, 3.5 cm and 2 cm in length, width and thickness respectively. All the *in-vitro* measurements were performed within 1-2 hours after excitation at ambient temperature consistent with other studies [35]. For *in-vitro* bioimpedance measurements, two Ag/AgCl pre-gelled disposable electrodes from Vermed (Vermed Inc., USA) were placed at two opposite sides of the cuboid samples (one electrode at the bottom and one electrode at the top sides of the samples). By means of a finger wearable capacitive pressure sensor on the examiner's finger, six constant force levels (2.2, 4.4, 6.7, 8.9, 11.1 and 13.3 N) were applied to the electrodes. While keeping the pressure approximately constant at each level, the multi-frequency bioimpedance data was collected in three trials.

The *in-vivo* experiment was performed on left and right forearm and bicep of 11 healthy human subjects. The subjects were three females and eight males aged 24 to 45. For the *in-vivo* experiment, two Ag/AgCl electrodes were integrated into a probe shown in figure 1. This probe was designed in SolidWorks and prototyped by a 3D printer. Two Ag/AgCl electrodes as well as six temperature sensors were integrated into this probe. However, the temperature sensors were not utilized in this study. The Ag/AgCl electrodes were at 2 cm constant distance. For the sake of consistency in the results, the tests were conducted on the same places of both hands. For bicep and forearm tests, the probe was placed at a distance 8 cm from elbow and wrist, respectively. The *in-vivo* data collection procedure was the same as the *in-vitro* testing. The only difference was that in the *in-vivo* experiments, the force levels were chosen so

that the pressure values were tolerable by human subjects. Thus, just three force levels (2.5, 5 and 7.5 N) were applied to the probe placed over the subjects' arms and biceps. The *in-vitro* and *in-vivo* admittances were measured at various force levels in three trials and recorded for further analysis.

Fig.1: a) The electrical impedance setup b) The electrical impedance spectroscopy (HF2IS) c) The designed and prototyped probe consisting of 2 Ag/AgCl electrodes and 6 temperature sensors (temperature electrodes were not used in this study)

Mechanical setup and procedure. Ten chicken breasts and two rat breasts (the same *in-vitro* breast samples used in the EIS experiment) were tested within five hours post-mortem interval, consistent with other studies [36–38]. To exclude the effect of fibers and, hence, anisotropic character of soft tissues in the study, samples were cut from transverse slices of the tissues in rectangular shape samples and compression testing was performed transversely perpendicular to the matrix of the fibers [2, 39–41]. Five samples from each chicken breast and one sample from each rat breast were prepared and compressed. The dimensions of the specimens were 15 mm, 8 mm and 6 mm in length, width and thickness respectively.

The mechanical characteristics of the chicken and rat samples were identified using an Electroforce 3200 (Bose Corp, Grand Prairie, MN) equipped with a 50 lbf load cell (Sensotec 31E, Honeywell Corp, Columbus, OH). The samples were compressed with polished aluminum platens at 0.1 N preload. Before applying the preload, drops of water were added to keep the samples hydrated and reduce friction between samples and platens. While preloading the samples, the surface contacts between the samples and platens were also checked visually. When the specimens were contacting well with the platens, the loading and unloading cycle was started. Chen *et al* found linear stress-strain curves up to 5% strain for cylindrical diverse tissue species and nonlinear behavior – once the strain exceeded 10% [42]. Thus, all the samples were compressed to 10% strain at a strain rate of 0.002 s⁻¹. The strain rate was kept constant when compressing the samples in order to exclude the effect of strain rate that would bring out the viscoelastic behavior of soft tissues [43]. The radial expansion of each specimen was visually monitored during the loading stage

in order to detect the occurrence of elastic-buckling or other irregular deformation. The samples that had undergone irregular deformation or buckling were removed from the study.

The mechanical characterization of tissue constituents was evaluated by capturing responses of forearm and biceps of healthy subjects to a compressive loading. The Pressure Profile System Fingertip Sensor was used to obtain force values through indentation. The displacement data was acquired via Celesco Cable Extension Transducers (SP2 Series, Celesco Transducer Products Inc., Chatsworth, CA).

Forearm and bicep of eleven healthy human subjects (the same *in-vivo* subjects used in the EIS measurements) were mechanically characterized via fingertip force sensor and Celesco spring pot. The spring pot was fixed over a piece of wood, and the rob end was fixed over the fingertip force sensor worn by the operator. As the index finger was moving towards the phantom, force and displacement data were measured simultaneously in real time.

Parameter fitting of Cole model in the form of admittance

The admittance of human tissue can be expressed by the Cole equation in the form of admittance proposed by [29]:

$$Y = G + jB = G_{\infty} + \frac{G_0 - G_{\infty}}{1 + \left(\frac{jf}{f_{yc}}\right)^{\alpha}} = \frac{1}{Z} \quad (1)$$

where Y is the whole admittance, G is the conductance and B is the susceptance. G_0 is the admittance at zero driving frequency, G_{∞} is the admittance when the driving frequency is infinity, f is the driving frequency, f_{yc} is the frequency at which the imaginary part of the admittance reaches its maximum and α is the dispersion parameter.

As stated by Liu *et al* [29], the equation of the admittance forms the equation of a circle and thus plotting the imaginary part of admittance (susceptance) versus the real part of admittance (conductance) in a complex plane results in a circular arc as shown in figure 2a.

Yang *et al* proposed an improved Least Absolute Deviation (LAD) method for data fitting and Cole feature extraction which is an alternative to the Least Square method [44]. The LAD method is an optimization method which minimizes the summation of the absolute errors which can be found by subtracting each data point from the fitted data [45].

$$\text{Fitness Func.} = \min \sum_{i=1}^n |e_i| = \sum_{i=1}^n |Y_{raw} - Y_{fitted}| \quad (2)$$

The BFGS quasi-newton method has been used in order to fit the data to the Cole model in the form of admittance [44]. This method aims to find the minimum of the fitness function shown in equation 2 considering the starting points as per Yang *et al*.

Fig.2: a) Imaginary part of admittance versus its real part (Cole arc). b) Cole model circuit.

Once the minimum of the equation 2 is found, the model is fitted to the Cole model and the four Cole features (G_0 , G_{∞} , α and f_{yc}) are extracted by this method.

The Cole model, figure 2b, models the tissue as a circuit including one resistor in series with one capacitor, and both in parallel with a resistor. If the capacitor is ideal, it will correspond to the Debye case with $\alpha=1$, resulting in a full semicircle in the complex plane. Using a constant phase element (CPE) instead will result in a depressed circular arc with $\alpha \neq 1$. The resistor and capacitor which are in series mimic the intracellular resistance (R_{int}) and bulk membrane capacitance (C_m) and the resistor in parallel with these two components mimics the extracellular resistance of tissue (R_{ext}). All these three Cole circuit parameters can be calculated by the following equations:

$$R_{ext} = R_0 \quad (3)$$

$$R_{int} = \frac{R_0 R_{\infty}}{R_0 - R_{\infty}} \quad (4)$$

$$C_m = \frac{1}{2 \pi f_c (R_{int} + R_{ext})} \quad (5)$$

$$\text{where } R_0 = \frac{1}{G_0}, R_{\infty} = \frac{1}{G_{\infty}} \text{ and } f_c = f_{yc} \alpha \sqrt{\frac{G_0}{G_{\infty}}}.$$

Modulus of elasticity measurements and indentation theory

In the present work, the indentation theories were applied for the *in-vivo* experiments considering soft tissue as an elastic layer bounded to a rigid body, which is deformed by a flat-ended cylindrical punch in the normal direction. The elastic modulus at each point of the indentation test was calculated using Hayes's theoretical solution [46]:

$$E = \frac{P (1 - \nu^2)}{2 D a \kappa(\nu, \frac{a}{h})} \quad (6)$$

where P is the indentation load, D is the indentation displacement, ν is Poisson's ratio, a is the radius of the indenter, h is the thickness of the tissue and κ is a factor which is a function of material properties and geometry of the tissue.

The average of stress distribution beneath the indenter was governed from the following equation [46, 47]:

$$\bar{\sigma} = \frac{1}{\pi a^2} \int_0^a \frac{P}{2\pi A \kappa} (a^2 - \rho^2)^{-\frac{1}{2}} 2\pi \rho d\rho \quad (7)$$

where ρ is the loaded location under the punch and the above equation is for $0 \leq \rho \leq a$. For $\rho > a$, $\sigma = 0$. κ is a factor which is a function of material properties and geometry of the tissue. The κ values corresponding to relative indentation and aspect ratios of the current study were calculated by doing some interpolations on the provided tables for different indentation levels [48]. The elastic modulus of the tissue within 10% relative indentation was obtained from the slope of stress distribution versus relative indentation curve.

Regarding the unconfined compression testing of chicken and rat breast, elastic moduli of the samples were acquired from the slope of the engineering stress versus strain and Hooke's law.

$$E = \frac{\sigma}{\varepsilon} \quad (8)$$

Results

Findings for electrical properties of tissue, feature extraction of Cole model by LAD, mechanical properties of tissue and the correlation of the electrical features and the displacement of tissue are given below.

Electrical properties of tissue extracted by LAD

For each sample/subject, the measurements were performed at each pressure level at three trials. If the acquired data at each of these three trials were not similar to the data of the two other trials due to any data acquisition error, that trial was excluded and the measured data of the two other trials were averaged. Knowing the applied current, the measured voltage and the sweeping frequency at each compression level and each trial, the admittance of the tested samples and subjects were calculated. For each sample/subject, the admittances of the three trials were then averaged within each compression level. Therefore, the average of raw admittance data of each sample/subject at each compression level were obtained. Fitting equation 1 to the averaged admittance Nyquist plots, resulted in the extracted Cole features (G_0 , G_∞ , a and f_{vc}) within each pressure level. Cole circuit equivalent parameters (R_{ext} , R_{int} and C_m) were then calculated from equations 3 to 5. Thus for all twenty chicken samples, two rat samples and eleven human subjects, R_{ext} , R_{int} and C_m were acquired at various pressure levels.

Table 1 represents the average of the Cole parameters of all subjects and samples at the first pressure levels (2.5 N in human subjects and 2.2 N in chicken and rat samples) and their standard deviation.

Mechanical properties of tissue

The mechanical experimental results demonstrated an approximate linear correlation between stress and strain in the unconfined chicken and rat tissue samples and an approximate linear correlation between stress and indentation in the confined human subjects' tissues. Figure 3 illustrates the stress versus indentation of bicep of one of the human subjects. This figure shows that by increasing the magnitude of the applied stress to the tissue, the magnitude of the resultant strain increases and there is an approximately linear relationship between the applied stress and the strain in soft tissue. Similar behavior was observed in all samples and subjects. The elastic moduli of human subjects were acquired from the correlation of stress versus indentation and by incorporating equation 6, and the elastic modulus of chicken and rat tissues were acquired from the correlation of stress versus strain and by incorporating equations 8. The mean modulus of elasticity of ten chicken breasts and two rat tissues are 36902.79 (N/m²) and 34810 (N/m²), respectively. The averaged elastic modulus of left and right forearm, left and right bicep of eleven human subjects are, 197641.6 (N/m²) and 193221.9 (N/m²), 165765.5 (N/m²) and 162921.7 (N/m²), respectively. These acquired elastic moduli will be used in the following section for correlating the changes of electrical properties and tissue displacements.

Fig.3: Stress versus indentation of *in-vivo* bicep of one subject.

Tissue displacement-dependent features analysis

Based on the modulus of elasticity of each type of tissue calculated in the previous section, the amount of displacement at each pressure level was calculated. The displacement of the unconfined tissues, chicken and rat, were measured by the Hooke's law and the displacement of the confined human subjects were calculated by the indentation theory. The extracted Cole features and subsequently the Cole circuit equivalent parameters at each pressure level were obtained in previous sections. The

Table 1. Averaged Cole parameters by LAD method at the first pressure level and the standard deviations

Samples or Subjects	Fitting Results		
	$R_{ext} (\Omega)$	$R_{int} (\Omega)$	$C_m (nF)$
Chicken Breasts	537.85 ± 23.19	512.34 ± 24.32	7.91 ± 0.50
Rat Breasts	565.54 ± 18.19	675.83 ± 98.93	30.7 ± 14.9
Left Forearms	2612508.42 ± 359731.87	986.46 ± 189.34	16.46 ± 6.19
Right Forearms	2125924.31 ± 189807.62	970.02 ± 183.89	18.45 ± 8.99
Left Biceps	7577699.16 ± 180562.62	1386.3 ± 299.1259	14.83 ± 7.65
Right Biceps	7563298.20 ± 121059.83	1252.9 ± 437.72	15.26 ± 8.53

extracellular resistance, intracellular resistance and membrane capacitance of each subject and sample were normalized to their corresponding values at the first compression level. These normalized parameters measured at each pressure level were then averaged and plotted against that pressure corresponding displacement in figures 4-9. These figures illustrate a linear relationship between the normalized Cole parameters and the displacement of tissue.

As figure 4 illustrates, at the maximum displacement of chicken tissue when the maximum force, 3 lb, is applied to the tissue samples, the normalized extracellular resistance increases 45% relative to its first value. Normalized intracellular resistance has a decrease of 20% and normalized membrane capacitance has an increase of 48% in chicken tissue. The changes in rat tissue includes an increase of 6% in normalized extracellular resistance, 7% decrease of normalized intracellular resistance and 17% increase of normalized membrane capacitance as observed in figure 5. Figures 6-9 indicate that at the maximum force applied to the human subjects, 7.5 N, the normalized extracellular resistance has an increase of 39.7% and 38.5% in left and right forearm and an increase of 294% and 297% in left and right bicep. At this point, the normalized intracellular resistance increases 8.8% and 8.9% in left and right forearm and 12.4% and 12.5% in left and right bicep. The decrease of normalized membrane capacitance in left and right forearm is 11.8% and 12.3% and in left and right bicep are 26.9% and 24.0% respectively.

Discussion and Conclusion

This study quantified the effect that compression has on the bioimpedance of soft tissue. Two types of experiments were conducted in this study, *in-vitro* and *in-vivo*. The results of this study show a linear correlation between the changes of electrical properties of tissue and its displacement in both *in-vivo* and *in-vitro* results. The Pearson products of the linear relationships ($0.918 < p < 0.999$) indicate that the electrical properties of soft tissue correlate well to the mechanical changes as samples and subjects are compressed. The difference in slopes and intercepts of the fitted models to the chicken, rat and human tissues data (figures 4 to 9) indicates that each type of tissue responds

differently to compression, suggesting that electro-mechanical relation of tissue may be affected by its type and structure.

Because of the high impedance of cell's membrane in lower frequencies, current flows between the cells and through the extracellular space, therefore the resistance measured at lower frequencies is mostly an indicator of the extracellular resistance. While at higher frequencies permeability of the cells' membrane increases, which allows current to cross the cell membrane, and therefore both intracellular and extracellular resistances of tissue influence the measured resistance. The Cole model of biological tissue also supports this idea by the fact that open circuit occurs at lower frequencies at branches containing capacitance and current flows only through the resistor called extracellular resistance and at higher frequencies, the capacitor short circuit occurs and current flows through both resistances in parallel. Accordingly, at higher frequencies, the equivalent resistance is comprised of two parallel resistors, which have a lower value compared to each resistor's value. Therefore, in general, the value of resistance at higher frequencies is less than lower frequencies regardless of type of tissue. This has also been observed in previous experiments by Boris-Reymond (1848-1860) [49] and in the current study, by the fact that the equivalent resistances at lower frequencies in chicken and rat breast are 537.85Ω and 565.54Ω and at higher frequencies are 262.39Ω and 307.89Ω respectively.

Based on the values of extracellular resistances in this study, it is postulated that the lower extracellular resistance reflects a narrower extracellular space in any type of tissue. Koshini *et al* also explained the increase in R_{ext} as a result of reduction in the extracellular volume [50]. The values at the first pressure level listed in table 1 indicate that the extracellular resistance of rat is higher compared to chicken, which according to this postulation it may be caused by the lower extracellular area between rat cells where current faces less space to travel through. This idea is supported by another experimental observation in which squamous epithelium tissue with more tightly packed cells shows higher resistance in lower frequencies compared to columnar and transitional epithelia, which have wider extracellular space [26]. The idea that the value of extracellular resistance is influenced by the space between

cells, may infer that applying pressure reduces the extracellular space and subsequently the extracellular resistance of tissue increases. This hypothesis is reflected in

the extracellular behavior under compression in both *in-vivo* and *in-vitro* results (part a's of figures 4 to 9).

Fig.4: Chicken breast tissue, the correlation of compression-dependent Cole parameters normalized to their values at the first pressure level and tissue displacements. (a) compression-dependent extracellular resistance versus tissue displacement. The correlation is: $Normalized R_{ext}=0.17 w+0.9$ and the Pearson product of the linear relationship is 0.972 (b) compression-dependent intracellular resistance versus tissue displacement. The correlation is: $Normalized R_{int}=-0.081 w+1$ and the Pearson product of the linear relationship is -0.986 (c) compression-dependent membrane capacitance versus tissue displacement. The correlation is: $Normalized C_m=0.19 w+0.91$ and the Pearson product of the linear relationship is 0.975.

Fig.5: Rat breast tissue, the correlation of compression-dependent Cole parameters normalized to their values at the first pressure level and tissue displacements. (a) compression-dependent extracellular resistance versus tissue displacement. The correlation is: $Normalized R_{ext}=0.031 w+0.99$ and the Pearson product of the linear relationship is 0.977 (b) compression-dependent intracellular resistance versus tissue displacement. The correlation is: $Normalized R_{int}=-0.033 w+1$ and the Pearson product of the linear relationship is -0.998 (c) compression-dependent membrane capacitance versus tissue displacement. The correlation is: $Normalized C_m=0.079 w+0.97$ and the Pearson product of the linear relationship is 0.992.

Fig.6: Left Forearm Tissue, the correlation of compression-dependent Cole parameters normalized to their values at the first pressure level and tissue displacements. (a) compression-dependent extracellular resistance versus tissue displacement. The correlation is: $Normalized R_{ext}=0.1 w+0.78$ and the Pearson product of the linear relationship is 0.983 (b) compression-dependent intracellular resistance versus tissue displacement. The correlation is: $Normalized R_{int}=0.023 w+0.95$ and the Pearson product of the linear relationship is 0.924 (c) compression-dependent membrane capacitance versus tissue displacement. The correlation is: $Normalized C_m=-0.031 w+1.1$ and the Pearson product of the linear relationship is -0.999.

Fig.7: Right Forearm Tissue, the correlation of compression-dependent Cole parameters normalized to their values at the first pressure level and tissue displacements. (a) compression-dependent extracellular resistance versus tissue displacement. The correlation is: $Normalized R_{ext}=0.1 w+0.76$ and the Pearson product of the linear relationship is 0.918 (b) compression-dependent intracellular resistance versus tissue displacement. The correlation is: $Normalized R_{int}=0.024 w+0.95$ and the Pearson product of the linear relationship is 0.993 (c) compression-dependent membrane capacitance versus tissue displacement. The correlation is: $Normalized C_m=-0.032 w+1.1$ and the Pearson product of the linear relationship is -0.997.

Fig.8: Left Bicep Tissue, the correlation of compression-dependent Cole parameters normalized to their values at the first pressure level and tissue displacements. (a) compression-dependent extracellular resistance versus tissue displacement. The correlation is: $Normalized R_{ext}=0.69 w-0.65$ and the Pearson product of the linear relationship is 0.979 (b) compression-dependent intracellular resistance versus tissue displacement. The correlation is: $Normalized R_{int}=0.029 w+0.93$ and the Pearson product of the linear relationship is 0.969 (c) compression-dependent membrane capacitance versus tissue displacement. The correlation is: $Normalized C_m=-0.063 w+1.1$ and the Pearson product of the linear relationship is -0.998.

Fig.9: Right Bicep Tissue, the correlation of compression-dependent Cole parameters normalized to their values at the first pressure level and tissue displacements. (a) compression-dependent extracellular resistance versus tissue displacement. The correlation is: $Normalized R_{ext}=0.7 w-0.77$ and the Pearson product of the linear relationship is 0.951 (b) compression-dependent intracellular resistance versus tissue displacement. The correlation is: $Normalized R_{int}=0.03 w+0.93$ and the Pearson product of the linear relationship is 0.986 (c) compression-dependent membrane capacitance versus tissue displacement. The correlation is: $Normalized C_m=-0.057 w+1.1$ and the Pearson product of the linear relationship is -0.987.

Another finding of this study was that while the changes in extracellular resistance have the same pattern in both *in-vivo* and *in-vitro* tests, the intracellular resistance and membrane capacitance show different behavior in *in-vivo* and *in-vitro* experiments. The *in-vivo* intracellular resistance increases as pressure is increased. The reason of increase in R_{int} could be the reduced intracellular space. Because the reduced intracellular space resists the current flowing cross the cells. This difference between the *in-vivo* and the *in-vitro* results may be because in the *in-vitro* tests, the samples are collected after the animals' death while in the *in-vivo* study, the subjects are alive and blood flow exists. When the blood supply is cut off in a tissue, the activity of ion pumps reduces and thus the distribution of ions and fluids between intracellular and extracellular spaces changes, which leads to cell swelling [51]. Cell swelling increases the intracellular volume and this could be a reason of reduction in the intracellular resistance in the *in-vitro* study. Cell swelling also reduces the extracellular pathways and makes them narrower, which is another evidence for the increase in the extracellular resistance [52]. Cell swelling and also release of Lysosomal enzymes in the cell, causes rupture in cell membrane [53]. In the post-mortem specimens, the cell membrane starts to deteriorate. Thus the cytosol leaves the cell and is mixed with the extracellular fluid [52]. This procedure is accelerated by applying pressure. The reduction in the intracellular fluid and the increase of the extracellular fluid (mixing the intracellular and extracellular fluid at the extracellular space) caused by deterioration of cell membrane and applying pressure might be another explanation of reduction in R_{int} and increase in R_{ext} . Demou also has mentioned the possibility of reshaping of cells from spherical to oblong orientation which may result in an increase or decrease in electrical properties of tissue [54].

Membrane capacitance in *in-vitro* experiments increases. The value of capacitance is proportional to the area of cell membranes and inversely proportional to the separation between sheets. Cell swelling and applying pressure increases the surface [51] and the cell membrane becomes thinner as a result of inflation [50]. Thus, a possible explanation for the reduction in membrane capacitance might be the decreased distance between two sheets of cell membrane and increased surface of these sheets. However, membrane capacitance decreases as the applied pressure to the *in-vivo* subjects is increased, which according to Dodde *et al* might be the result of contacting the cell membranes [25].

In this study, the changes in electrical properties of living tissue were also compared contra-laterally. The results illustrate the same behavior and the same linear correlation in contra-lateral parts of human subjects. This observation suggests the idea that the correlation of electrical-mechanical properties of one part of body is the same as its contra-lateral part unless there is an abnormality in one of the contra-lateral parts. This comparison of electrical-mechanical correlation of contra-lateral parts of

the body may be considered as a method for diagnosis of tumor or any abnormalities within tissue.

The results of *in-vivo* and *in-vitro* strengthen the fact that EIS measurements of *in-vitro* experiments do not represent an exact *in-vivo* environment. This idea insists on performing more experiments *in-vivo* rather than *in-vitro* in order to get more reliable results in the field of electrical impedance spectroscopy. One possibility for different behavior of *in-vivo* and *in-vitro* results would be the blood flow in the *in-vivo* case. The flowing blood in the living tissue is the most important factor influencing the tissue impedance. Since there is no blood flowing in dead tissue, the changes of its impedance properties do not follow the same pattern as the living tissue.

However, the findings of the current study do not fully support the previous research by Dodde [25]. The reason for this inconsistency may arise from the difference in the experiment protocols of these two studies, thus this is an important issue for future research. Further research should be done to investigate the effect of pressure on electrical properties of tissue both *in-vivo* and *in-vitro*.

This study also suggests the idea of modifying the Cole model. In the Cole model, the tissue equivalent resistance and capacitance values are constant while according to this study a modified Cole model should be used in which the parameters are dependent on tissue displacement and elasticity.

There were also some limitations in this study, which should be eliminated during further experiments. In the *in-vitro* experiment, the tissues were tested on a firm foundation and samples were not supported by surrounding tissue and bone while there were not the same conditions in the *in-vivo* tests. Another limitation of this study is that all the experiments were performed in the room temperature and there is a possibility that the room temperature was not constant during the experiments. As shown by Schwan and Foster, the electrical conductivity of tissue is dependent on temperature [55].

Acknowledgements

Financial support of this project was provided by the Natural Sciences and Engineering Council of Canada (NSERC). The authors would like to thank Ehsan Daneshi Kohan and Shima Zaeimdar for their help in progress of this project.

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