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Use of Vibrational Optical Coherence Tomography to Determine Mechanical Properties of Cells and Tissues *in Vivo*

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Abstract

The ability to measure the elastic and viscous mechanical properties of cells and tissues *in vivo* is important to understand the pathobiology of development, maturation, and diseases. Using vibrational optical coherence tomography (VOCT) my lab has developed a noninvasive technique to measure the elastic and viscous properties of cells, tissues, and implant materials both *in vitro* and *in vivo*. The results measured using VOCT suggest that the elastic modulus of isolated cells reported *in vitro* is much smaller than that of cells in series with other cells and extracellular matrix *in vivo*. At low strains the loss moduli of cells and tissues *in vivo* is strain rate dependent and decreases with increased strain rates above a strain rate of about 100 cycles/sec. The high viscous component of the mechanical behavior of soft tissues at low loading frequencies provides a physiologic mechanism to dissipate energy applied to soft tissues minimizing premature mechanical failure. Changes in elastic moduli exhibited by cells, blood vessels, and fibrous tissues can be followed during disease progression *in vivo* noninvasively. It is concluded that VOCT offers advantages over other methods for measuring mechanical properties of cells and tissues *in vivo*.

Keywords

Elastic Modulus, Viscous Loss, Energy Dissipation, Extracellular Matrix, Cells, Collagen, Fibrotic Tissue

1. Introduction

The mechanical properties of cells and tissues play critical processes in maintain-

ing organ and tissue homeostasis in mammals. These include growth, differentiation, migration, and processes involved in mechanotransduction [1] [2]. Mechanical property changes can serve as disease biomarkers and help track disease progression [3], modify tissue shape and organ development during growth [4], affect cell division and produce changes in the cell and nuclear cytoskeletons [4] [5], and maintain normal cell and tissue structure [6].

There have been several recent reviews that summarize testing methods used to study the mechanical properties of cells and tissues in the laboratory and *in vivo* [7]-[12]. Methods such as AFM, particle-tracking microrheology, optical tweezers/stretching, magnetic tweezers/twisting cytometry, optical coherence tomography, microfluidics, micropipette aspiration, elastography, tensile testing, and Brouillon light scattering have been widely utilized to measure the mechanical properties of single cells and tissues [7]-[13]. Studies have demonstrated notable differences between aging cells, including erythrocytes, leukocytes, endothelial cells, cardiomyocytes, osteocytes, and epithelial cells, when compared to their younger counterparts [7]. Mechanical measurement techniques can be put into two categories: those that can be used to apply controlled deformations and forces to cells and tissues, and those that monitor the ability of a cell and tissues to generate forces and deform their environment [12]. The structure and the mechanical response of tissues and organs, as well as constitutive formulations have been used to support continuum biomechanical studies [9]. The information generated by many of these techniques is pertinent to understanding the mechanical behavior of cells and tissues *in vitro* but the relevance of these studies to *in vivo* behavior is still unclear.

Understanding the behavior of cells and tissues *in vivo* requires recognition that cells and soft tissues are highly viscoelastic and therefore cannot be treated like elastic solids; therefore, the usefulness of analysis of their behavior using classical continuum mechanics is questionable [2] [13]-[26]. Different approaches used have led to published modulus values for cells and soft tissues that range from several Kpas to values that reach 100s and 1000s of MPas [15]-[18]. Tissues like skin and cornea have low strain elastic moduli like crosslinked silicone rubber; the modulus of the latter material is controlled by the crosslinking time and density [14]. If cells and tissues have elastic moduli much lower than that of soft synthetic polymers they would tear easily when adhesive tape is applied to skin or when normal forces impact the cornea. These considerations must be understood when discussing the mechanical properties of cells and tissues.

2. Measurement Techniques and Their Limitations

There are several limitations associated with measurement of cell and tissue mechanical properties that must be overcome to compute reasonable modulus estimates that can be used to understand the molecular basis of mechanical properties of cells and tissues *in vivo*. (1) Both cells and tissues are highly viscoelastic meaning that their mechanical properties are strain and time dependent [13] [15] [18];

(2) neither cells nor tissues are found isolated in mammals except in blood and in some interstitial spaces; and (3) the ability to relate *in vitro* and *in vivo* behaviors is quite complicated since most cells are directly connected to other cells and/or the surrounding extracellular matrix (ECM) [2] [16]. Isolated cells have mechanical properties that are quite different than cells connected into continuous cross-linked mechanical networks with other cells and ECM [16]. Therefore, unless the effects of strain, strain rate, cell-cell, and cell-tissue connections are considered the mechanical properties measured *in vitro* will have little relevance to behavior *in vivo*. Therefore, the wide range of elastic moduli reported for cells and tissues may reflect the need to consider interactions between cells and other tissue components that exist *in vivo*. These considerations must be explored to understand the molecular and tissue behavior of cells and tissues in health and disease.

Other problems that lead to errors in calculated values of cell and tissue moduli include the following assumptions: (1) Poisson's ratio is 0.5 for elastic modulus calculations; (2) soft tissues are quasi-linearly viscoelastic at strains greater than about 10% [19]; and that the viscous component of the behavior is not significant at strain rates below 100 cycles per second [15]. Therefore, any new method to compute the elastic and viscous properties of cells and soft tissues *in vivo* needs to consider how to measure: (1) the elastic and viscous components of the tissue behavior separately; (2) the low strain behavior of cells and tissues at high strain rates above 100 cycles per second; (3) how to calibrate any new method for measurements made *in vivo* with a gold or other standard; and (4) how to perform these measurements noninvasively *in vivo*. In this paper, we will review how these conditions can be approached using a new technique termed vibrational optical coherence tomography (VOCT).

3. Methods

3.1. Theoretical Basis of VOCT

The ability to measure the mechanical properties of highly viscoelastic materials such as cells and soft tissues requires observation of the instantaneous (elastic properties) and time dependent (viscous properties) properties of tissues and materials at low strains where the material will be in the linear region of the stress-strain curve. For soft polymeric materials like silicone rubber this is not a requirement since the viscous component of the modulus is approximately constant and contributes only about 10% to the elastic modulus values measured [14]. However, this is not true for soft tissues since when they change their shapes and exude fluid into the interstitial spaces at low strain rates which causes a change in Poisson's ratio. This behavior influences mechanotransduction pathways leading to changes in cell division, changes in DNA, and protein synthesis [16]. At low strain rates, viscous behavior can alter the modulus value up to about 50% due to fluid movement and cellular behavior during mechanical loading [16]. One way of quantitatively assessing these changes is by measuring the changes in the resonant frequency of a material at different strain rates [19] [23]. The resonant frequency

of tissue is the frequency at which the material undergoes its maximum displacement and energy storage occurs in almost a purely elastic manner.

Resonance is a phenomenon in physics, that defines that a system will oscillate with a greater amplitude at specific frequencies [27]. These frequencies, known as resonant frequencies, represent inherent properties of the material determined by the physical characteristics and configuration [2]. At the resonant frequency of a polymeric material large amounts of energy are stored in reversible backbone bond angle and molecular length changes [28]. In collagenous tissues this occurs by stretching the flexible regions at the molecular and fibrillar levels [29] Measurement of tissue component resonant frequencies *in vivo*, including that of cells and other macromolecular structures, provides "real life" values of the elastic modulus which are different from the mechanical properties of isolated cells and macromolecules.

The maximum displacement of a mechanically loaded sample occurs during elastic deformation. This condition is where little energy is lost due to friction, fluid flow, or molecular sliding. Using optical coherence tomography (OCT) changes in tissue dimensions can be obtained instantaneously at varying applied deformations [17] [18]. Using OCT an image is formed from reflected infrared light from the sample. At deformation rates up to as high as several thousand cycles per second instantaneous deformation can be measured from the image formed [17] [18]. From studies at different deformation rates the resonant frequency can be determined from the frequency at which the maximum deformation occurs. In multilayered materials each layer will have its own resonant frequency characteristic of the properties of that part of the tissue [19] [20]. In skin the epidermis, papillary collagen, and blood vessels all have characteristic resonant frequencies that change because of skin pathology [19] [20].

Measurement of the resonant frequency of a tissue can then be related to the composition by reviewing the images created by OCT at different loading frequencies [19] [20]. Calibration of VOCT measurements on a material is accomplished by: (1) instantaneous stress-strain measurements of the behavior of a tensile sample measured using a load cell and micrometer; and (2) by measuring the resonant frequency and thickness of the same sample at the same time [19] [20]. These measurements can then be used to create a calibration curve that leads to the development of a relationship between E, the elastic modulus, the sample thickness d, and the resonant frequency, fn, as shown in equation (1) for soft tissues and synthetic polymers with densities close to 1.0.

The relationship is developed by comparing tensile stress-strain measurements (E) to resonant frequency (fn) measurements on the same material at the same time for sample thickness (d) measured from the OCT image or with a micrometer (see equation 1) [19] [20]. VOCT measurements made on synthetic polymers and soft tissues (see **Table 1**) were used to develop equation (1):

$$\textbf{Soft Tissues:}\quad \mathrm{Exd} = 0.0651 \times \left(f\ n^2 \right) + 233.16 \tag{1}$$

3.2. Experimental VOCT Measurements

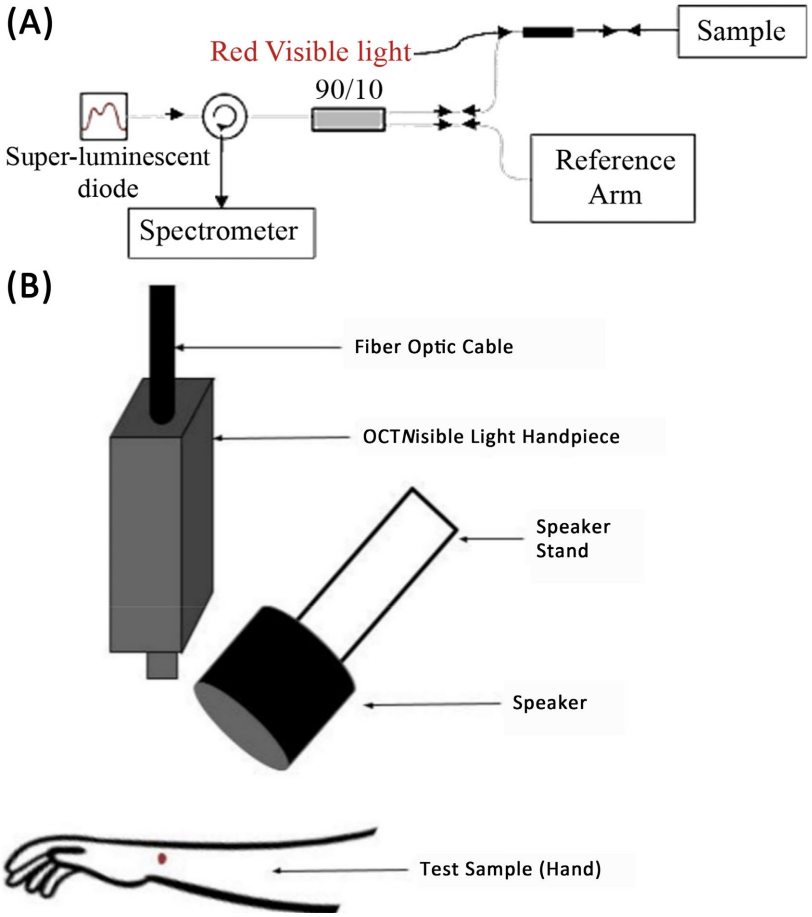

Figure 1. (A) Block diagram of the setup of an OCT device modified to do vibrational optical coherence tomography (VOCT). The speaker shown is about 2 inches in diameter and provides audible sound through a computer-driven app to vibrate the sample between 30 and 300 Hz for skin. The displacement of the sample at each frequency is obtained from amplitude data collected and stored from raw images created by the OCT. The sample displacement is divided by the displacement induced by the speaker in the absence of the sample to correct for speaker induced vibrations. (B) Schematic drawing of the OCT handpiece used to collect the VOCT data at each frequency on skin and other soft tissues *in vivo*.

Resonant frequency measurements and elastic modulus calculations on different tissues can be collected by vibrating the sample using sound from an acoustic speaker at fixed frequencies between 30 and up to 1000 Hz and then collecting the instantaneous image of the sample at each frequency [19] [20]. The measurement reported in this paper are synthesized into final form from previous publications [13]-[26]. During resonant frequency measurements the sample is continuously loaded by an acoustic signal generated by a speaker through an app on the OCT unit. **Figure 1** shows a block diagram of the system used to measure the resonant frequency of a tissue. Typically for soft tissues acoustic vibrations between 30 Hz to 500 Hz are used to measure the resonant frequency (s) of most soft tissues. While the applied vibrational frequency and sample vibrational frequency are the

same, the resulting sample component deformation will depend on the sample material properties. The displacement of the sample at these frequencies is very small. Collagenous soft tissues operate *in vivo* in the linear low modulus region of the stress-strain curve [21] [22]. For collagenous tissue such as skin and cornea, the *in vivo* strain has been estimated to be about 5% [21]. A strain between 5% and 10% falls into the low modulus or toe region of the collagen tensile stress-strain curves of these tissues [21]. At strain rates above 100 Hz (the resonant frequency of collagen in many soft tissues *in vivo*), the viscous component decreases and approaches a value of about 5% of the value of elastic modulus at high frequencies. At high frequencies the modulus becomes almost purely elastic as has been shown for skin and cornea [15] [17]. The modulus calculated from the resonant frequency is due to storage of elastic energy which reflects only bond stretching and not molecular and fibrillar slippage as well as rearrangement of the attached and surrounding fluid which is responsible for the viscous component of the behavior [15] [17]. At low frequencies intermolecular and interfibrillar fluid flow and cellular deformation behavior in living tissues is associated with a large viscous component. At high frequencies above 100 Hz the fluid and cells do not have enough time to alter their shapes and location and the behavior becomes almost purely elastic.

3.3. Measurement of Tissue Resonant Frequency-Initial Proof of Concept

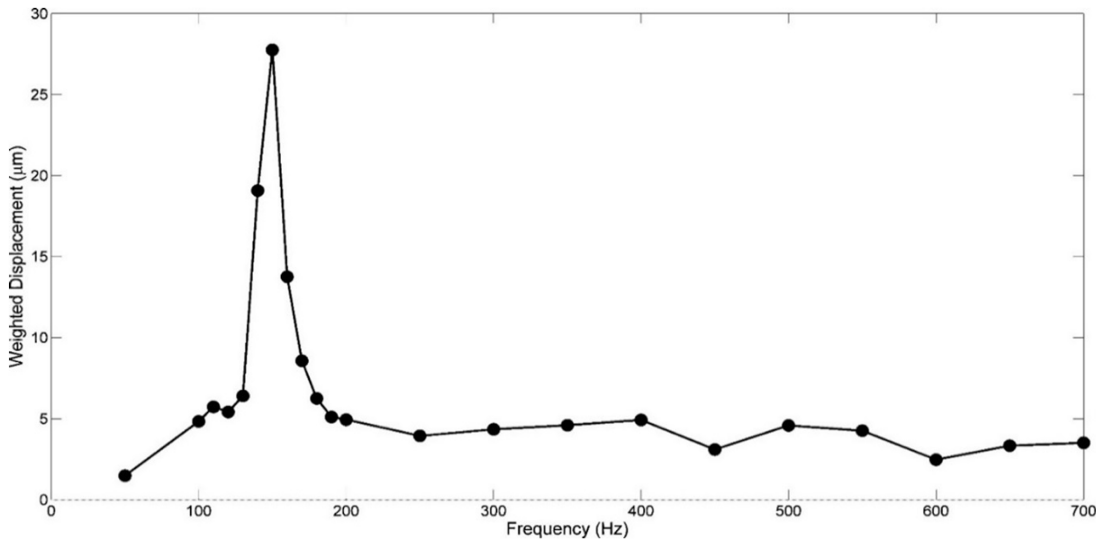

Figure 2. Weighted displacement versus frequency for decellularized human dermis. The frequency at which the maximum displacement of a sample occurs is defined as the resonant frequency and is related to the elastic modulus of a material (see equation 1). Note the sharpness of the peak defines the material uniformity. The weighted displacement versus frequency data shown is for decellularized human dermis, which has a modulus of about 2 MPa at a strain of 5% *in vitro*. The weighted displacement is the displacement of the sample divided by the displacement in the absence of the sample due to speaker vibrations. Note that the elastic modulus is estimated by using equation (1) after the thickness (d) is measured either using a micrometer or from OCT images. Measurements on purified dermal collagen, skin, cartilage, cornea, silicone rubber and other synthetic polymers were used to develop equation (1). VOCT measurements and tensile measurements made on the same material at the same time were used to verify the relationship.

The easiest way to explain how resonant frequency data is measured is to start with a simple system that is composed of pure collagen. Decellularized human skin is made up of collagen types I and III after the cells and DNA are removed [21]. Using this material the resonant frequency can be measured by vibrating the sample with sound from an acoustic speaker at frequencies between 50 and 300 Hz. The resonant frequency is the frequency at which the maximum displacement is observed which in this case is about 150 Hz (see **Figure 2**). The weighted displacement is the ratio of the observed displacement with the sample present divided by the displacement without the sample present. The speaker has its own resonant frequencies that must be considered when testing a tissue sample. Once the resonant frequency is measured the elastic modulus can be calculated using equation 1 after the sample thickness is measured.

3.4. Measurement of Resonant Frequency of Skin *in Vivo*

The same approach can be used to measure the resonant frequency of skin *in vivo* which is composed of cells, papillary collagen, and blood vessels. **Figure 3** shows the weighted displacement versus frequency for normal skin and scar tissue illustrating the increased resonant frequency seen in scar tissue compared to normal skin [22]. Note cells and blood vessels in normal skin *in vivo* are usually minor components of the tissue and do not show displacement peaks at 50 and 150 Hz in some locations. Pathological scar tissues are characterized by altered cross linking making them stiffer [22]. This explains the increased resonant frequency difference seen when comparing normal skin and scar.

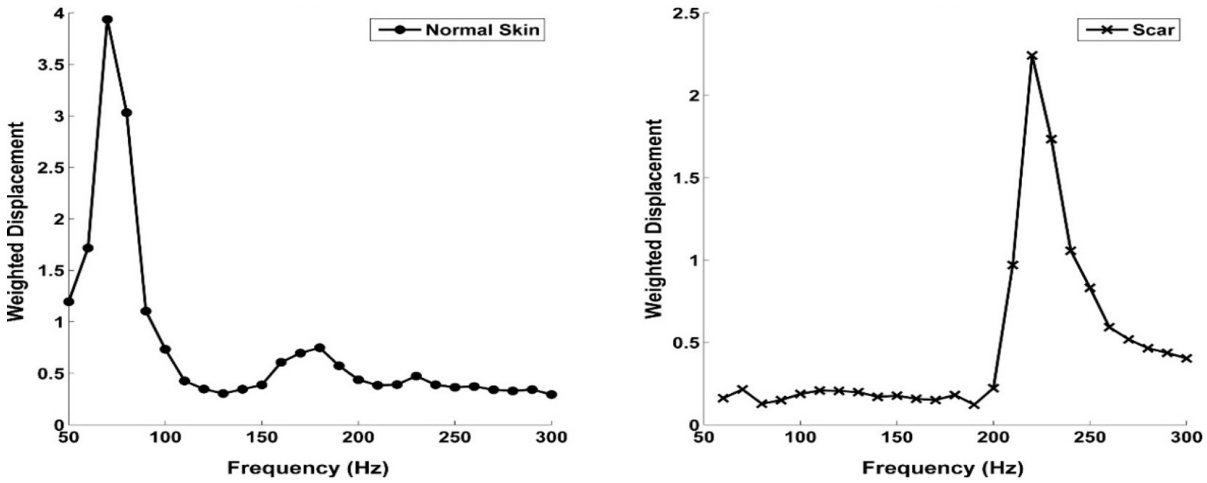

Figure 3. Weighted displacement versus frequently for human skin (left) and scar (right) measured *in vivo*. The elastic modulus of normal skin with a resonant frequency of 90 to 100 Hz is about 2.5 MPa and that of scar with a resonant frequency of about 240 - 250 Hz is between 6 and 10 MPa. The resonant frequency of normal skin is much lower than that of neighboring scar tissue. Using this approach the resonant frequency of a variety of materials, cells, and tissues can been characterized *in vivo*.

When the elastic modulus is studied for a variety of tissues using VOCT it has been observed that each tissue component has a "characteristic" modulus that is

observed for each tissue component (see Figure 4 and Table 1). The cellular resonant frequency of normal epithelial and most cells *in vivo* is about 50 - 60 Hz yielding an elastic modulus of about 1.0 MPa in skin and cornea [20] [22]. Cancer associated fibroblasts are somewhat stiffer in basal and squamous cell carcinomas, and melanoma. These fibroblasts have a resonant frequency *in vivo* of about 70-80 Hz and have moduli of about 1.2 MPa [23]-[25]. This contributes to the stiffening of cancerous skin lesions. There is a proliferation of normal epithelial cells and cancer associated fibroblasts in all these three types of skin cancers [23]-[25]. Cancer associated fibroblasts are stiffer than normal cells because of increased connections with neighboring cells and fibrotic tissues compared to normal epithelial cells.

Table 1. Resonant frequency peaks and their associated moduli based on VOCT measurements [26].

Tissue	Resonant frequency (Hz) {SD}	Modulus E (MPa) {SD}
Lamellar bone	990 {10.00}	173 {20}
Subchondral bone	586 {26.07}	67.81 {11.11}
Ear and L. nasal cartilage	290 {14.14}	16.2 {1.74}
Upper nasal cartilage	380 {14.14}	30.4 {5.89}
Fat, epidermal cells	40-70 {12.90}	1.110 {0.25}
Fibrotic tissue	210 {10}	10.84 {2.48}
Anterior cruciate ligament (ACL)	525 {7.07}	53.9 {2.25}
Meniscus	430 {14.14}	31.4 {3.37}
Bicep muscle	378 {16.02}	29.6 {2.62}
Quadriceps muscle	365 {21.21}	20.5 {2.32}
Nerve	266 {11.54}	15.86 {2.24}
Normal skin	110 {7.38}	2.15 {0.29}
Cornea, sclera	140 {14.14}	2.4 {0.14}
Achilles tendon	440 {10.00}	34.0 {5.98}
Flexor digitorum tendon	370 {14.14}	22.7 {9.42}
Patellar tendon	430 {5.77}	33.8 {4.62}
Vascular carotid artery	136 {11.54}	4.64 {0.98}
Radial artery	155 {11.98}	3.66 {0.65}
Vein	165 {7.07}	4.84 {0.025}

Note: SD = standard deviation.

The viscous behavior of cells is much greater than the viscous behavior of collagen in tissues and contributes to energy dissipation that prevents soft tissue injury and failure. Loss of cells and proteoglycans from decellularized human der-

mis transform skin from a flexible material into a brittle stiff material that fails at lower strains. This partially explains the loss of skin's ability to resist tearing in older individuals where collagen fiber fragmentation and loss of proteoglycans occur.

Synthetic polymers and natural tissues all have characteristic resonant frequencies that differ based on the differences in the molecular and supramolecular compositions of the materials [20]. Since each tissue has a "characteristic" resonant frequency and elastic modulus, the mechanical properties of cells and tissues in different disease states can be measured and related to changes in cellular and tissue compositions.

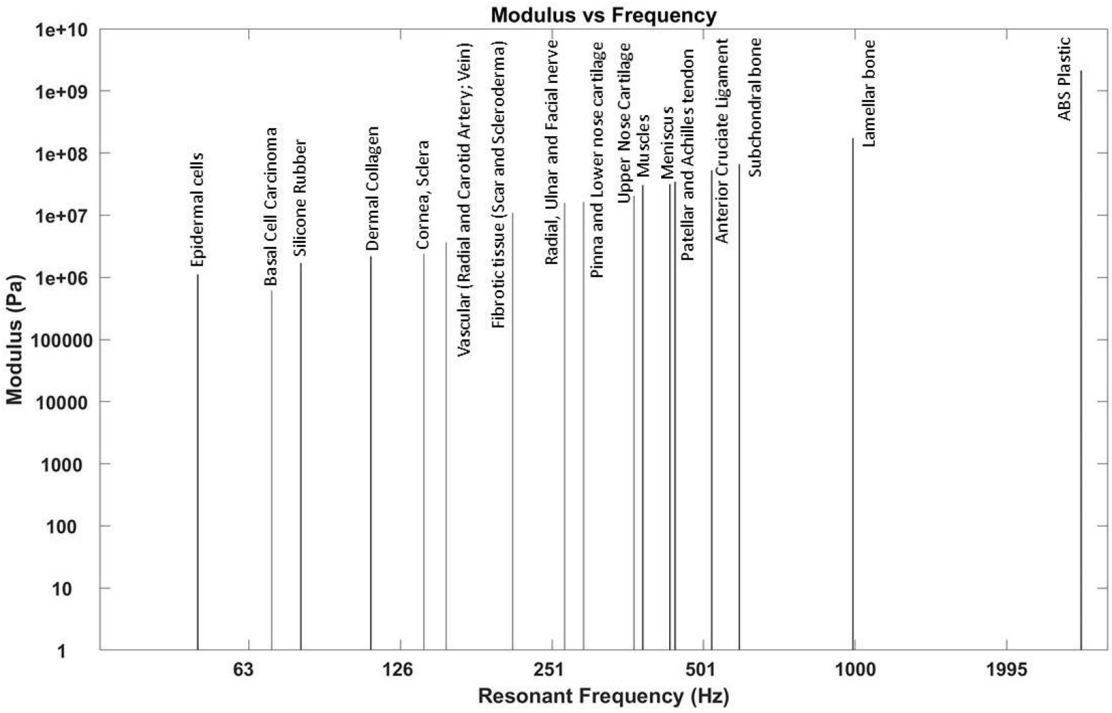

Figure 4. Plot of log of the elastic modulus for cells, tissues, and synthetic polymers derived from VOCT measurements made both *in vitro* and *in vivo*. The relationship between E and d for the different materials were determined experimentally and only soft tissues follow equation (1) since the density of bone and synthetic polymers is different than 1.0 gm/cc.

3.5. Changes in Elastic Modulus Associated with Skin Cancer

One of the important uses of VOCT is to follow the changes in mechanical properties of tissues associated with progression of diseases noninvasively. A good example of this is the stiffening of both cancer associated fibroblasts and fibrotic tissue associated with skin cancer formation as well as softening of new thin blood vessels. VOCT measurements made on normal skin *in vivo* are characterized by several peaks (see **Figure 5**). In normal skin, a small cellular peak occurs usually at about 50 Hz, a papillary collagen peak at about 100 Hz, a blood vessel peak at about 150 Hz. Sometimes fibrous peaks are seen at 180 - 250 Hz in skin cancers [23]-[25] (see **Figure 5** and **Figure 6**).

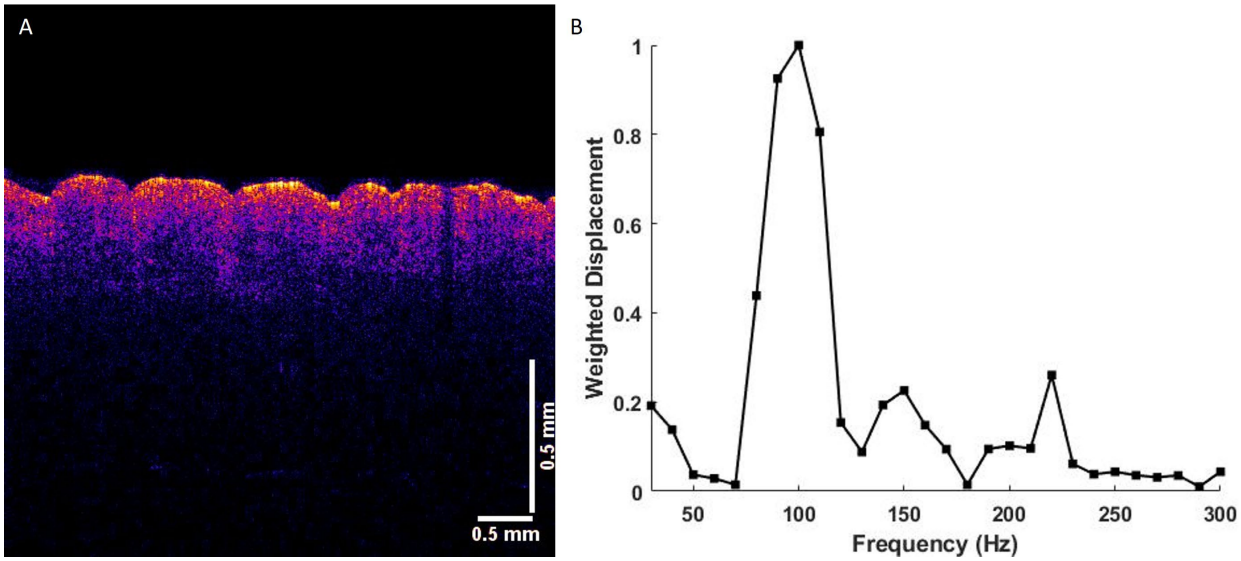

Figure 5. (A) A 2D color-coded OCT image of a cross-section of normal skin *in vivo* characterized by a yellow stratum corneum layer, pink and red granulating cell layers, and blue papillary and basal cell layers. (B) A plot of weighted displacement versus frequency for normal skin. Note the peaks at about 50 Hz (cells), 100 Hz (dermal collagen), and 150 Hz (blood vessels) are found in normal skin. The peak at 220Hz reflects some fibrous tissue present. The cells are found primarily in the epidermis and papillary dermis, while the dermal collagen and blood vessels are found in the papillary dermis based on tissue histology [25].

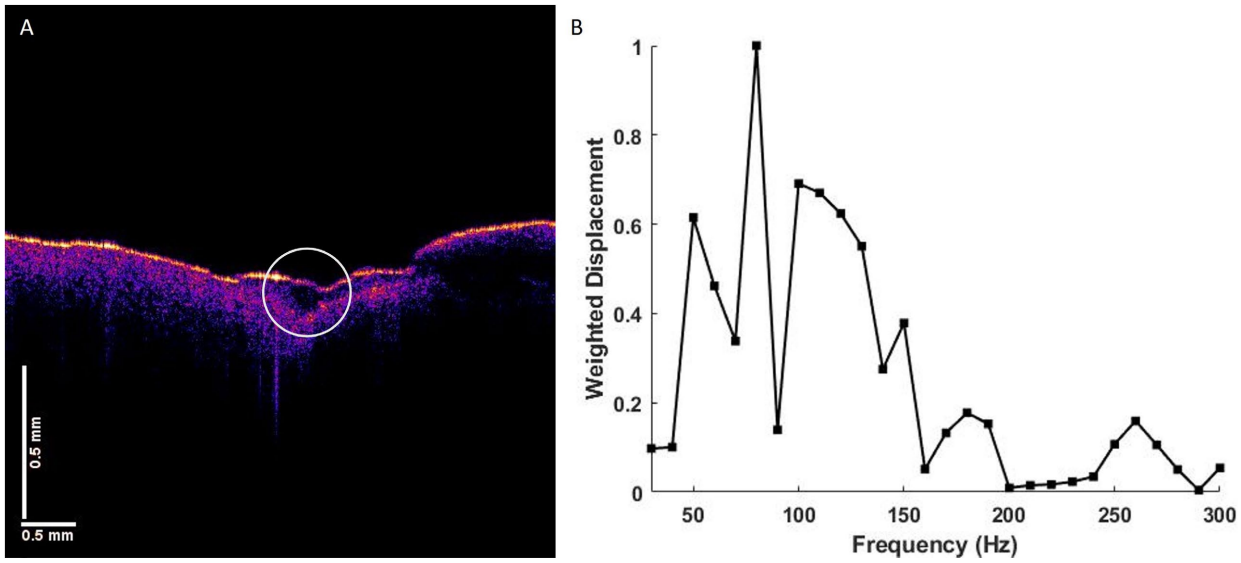

Figure 6. OCT image and VOCT weighted displacement versus frequency plots from a lesion diagnosed as a melanoma by a board-certified dermatopathologist**.** (A) 2D color coded cross-sectional OCT image of a cancerous melanoma (see circle). (B) Plot of weighted displacement versus frequency showing the mechanovibrational peaks. The change in size of the peaks at 80 Hz (cancer associated fibroblasts), 130 Hz (new thin blood vessels), and fibrous tissue at about 260 Hz are characteristic of all types of skin cancers including melanoma, basal cell carcinomas, and squamous cell carcinomas. The color coding of the OCT image was accomplished based on the pixel intensity and use of a look-table to assign the colors. The diagnosis of this lesion was based on histopathological review of the lesion by a board-certified dermatopathologist. Note the mechanovibrational data in B used to characterize cancerous lesions is supported by convolutional neural networks and AI analysis used to characterize the cancers [25].

When VOCT is used to study cancerous tissue the color-coded OCT image (see **Figure 6(A)**) and spectrum of resonant frequencies change (compare **Figures**

5(B) and Figure 6(B)). The color coding of the OCT image was accomplished based on the pixel intensity and a look-table to assign the colors. There are new peaks at 70 - 80 Hz (cancer associated fibroblasts), new thin cancer associated blood vessels (130 Hz), and a fibrotic collagen peak occurs at 250 - 260. The change in resonant frequency of cells (80 Hz), new thin blood vessels (130 Hz), and fibrotic collagen (250 - 260 Hz) is observed in all cancerous lesions including BCC, SCC, and melanoma.

3.6. VOCT Viscoelastic Measurements Made on Soft Tissues and Polymers

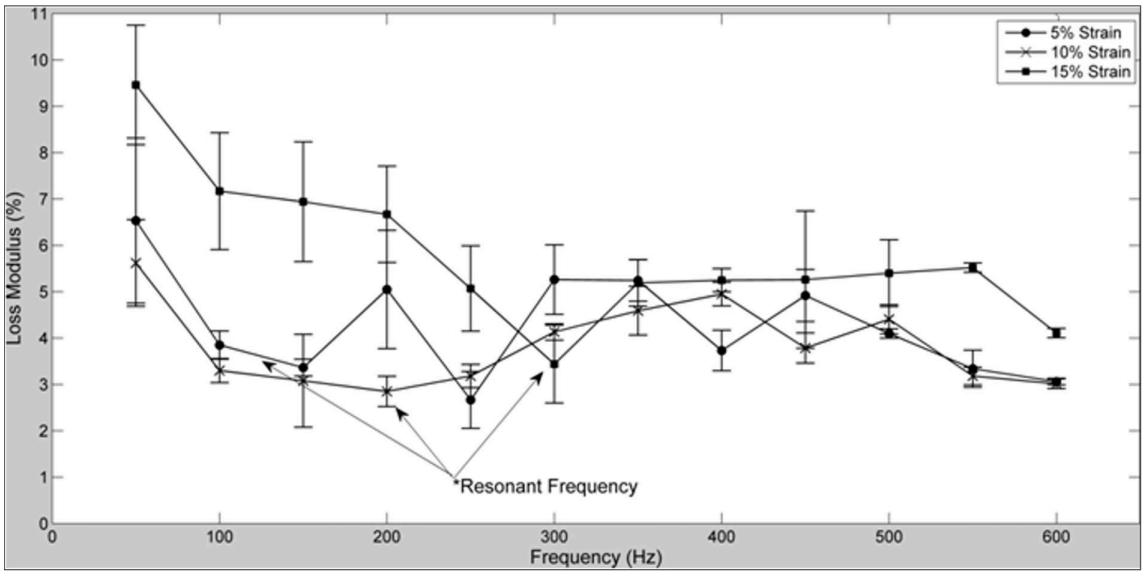

Figure 7. A plot of the loss modulus determined from VOCT relaxation experiments as a percentage of the elastic modulus of decellularized human dermis *in vitro* as a function of vibrational frequency and strain. Note the loss modulus of decelluarized dermis does not change much with increasing strain. The loss modulus is low for pure collagen fibers in decellularized human skin compared to normal skin *in vivo* and is like that of synthetic rubbery polymers. This viscous behavior of stretched collagen fibers is like that seen for silicone rubber (data not shown); the loss modulus of silicone rubber is almost independent of strain and is about 10%. Note the absence of proteoglycans and cells in decellularized dermal collagen reduces the viscous component and the viscoelastic behavior (see Figure 8). The data shown was collected on 5 samples of decellularized dermis.

To measure the viscoelasticity of soft tissues and polymers the VOCT loading conditions are different than for elastic tissue measurements. In the viscoelastic experiment for determination of the viscous response, the sample is cycled through at least three acoustic loading cycles and then the acoustic loading is terminated. The loss modulus is estimated from the half width of the decay of the weighted displacement versus time. The viscous component is obtained by dividing the change in frequency at the half height of the mechanovibrational peak, or 3 decibels down from the maximum peak in the power spectrum, by the driving frequency. This method is known as the half-height bandwidth method [22]. This approach follows the delay in the relaxation which is related to the viscous behavior of the sample. A longer decay in a viscoelastic material is associated with a

larger half width of the weighted displacement versus frequency curve. Figure 7 shows the relationship between loss modulus and frequency for decellularized human skin *in vitro* at different applied strains.

Figure 8 shows the loss modulus for human skin measured noninvasively *in vivo* using VOCT [22]. The loss modulus is greater in normal skin *in vivo* compared to decellularized human dermis *in vitro*. The increased viscous component of normal skin compared to decellularized dermal collagen is likely due to cell contractile forces exerted on cells connected in series together and due to the presence of proteoglycans. In addition, the influence of proteoglycans present of the surface of collagen fibrils and fibers provides some interfibrillar slippage. The rearrangement of intermolecular and interfibrillar fluid also contributes to the viscous behavior at low strain rates. This increased viscous behavior at low strain rates prevents skin from tearing during stretching and dissipates applied energy.

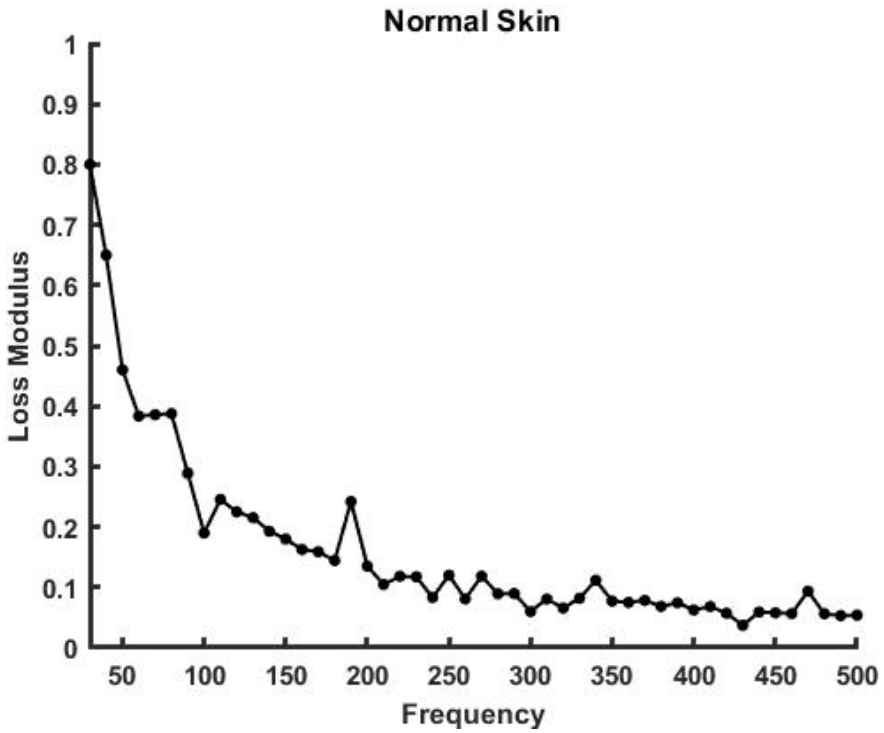

Figure 8. Loss modulus of normal skin measured using a VOCT relaxation test conducted *in vivo*. The data for the loss modulus is shown as a fraction of the elastic modulus versus frequency in Hz for normal human skin. Note the maximum loss is found for skin components at frequencies less than 50 Hz. The high loss modulus observed at low frequencies is a result of rearrangement of the viscous interfibrillar materials, fluid flow, and the cellular contribution to the viscoelasticity of skin. At low strain rates cells can respond to provide a response to an applied load whereas at high strain rates the cells behave as rigid elements and cannot dissipate enough energy to prevent skin tearing. Viscous energy loss by muscle and tendon *in vivo* is like that of skin and is an important means of energy dissipation in soft tissues that limits premature mechanical failure. This also is true in the cornea which protects the components of the anterior and posterior segments of the eye from low frequency mechanical damage [15] (see Figure 9).

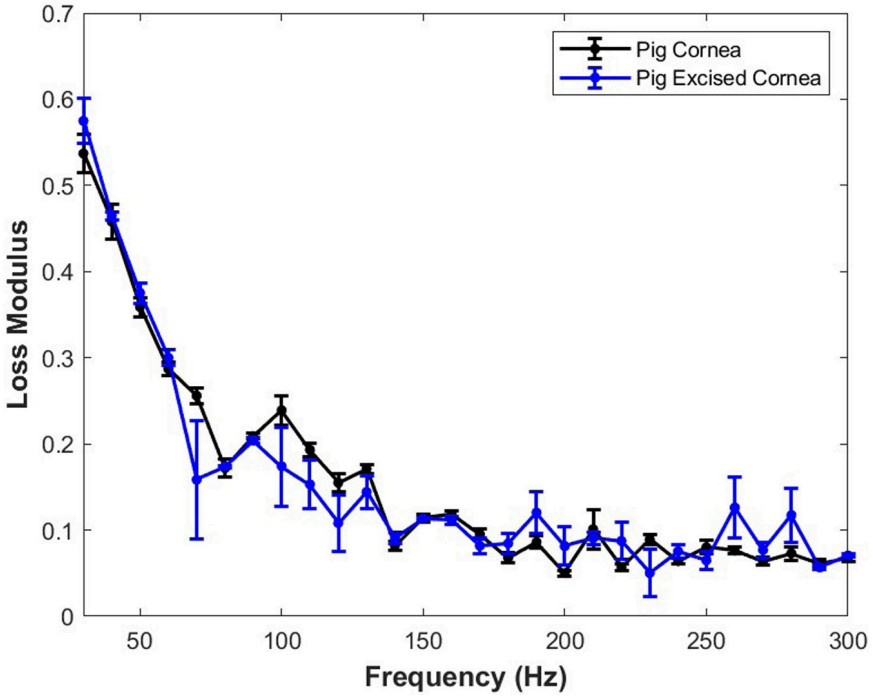

Figure 9. A plot of loss modulus as a fraction of the elastic modulus versus frequency for whole pig globe from measurements on the cornea versus excised cornea *in vitro* determined using VOCT. These measurements were conducted on at least 5 samples of each tissue after pulsing the sample with acoustic sound and then making measurements directly after removing the acoustic signal. Note the loss moduli decrease with increasing frequency and is similar in pig globes and excised corneas and in human tissue *in vivo*. At low mechanical loading frequencies, the cornea is highly viscoelastic and dissipates forces and energy applied to the eye. Therefore, mechanical measurements made at frequencies below 100 Hz need to be corrected for frequency and strain-rate dependence.

4. Discussion

There have been many published papers on the mechanical properties of cells and tissues in the literature. Most of these papers make measurements on isolated cells and tissues *in vitro* and assume that *in vitro* measurements have relevance to tissue behavior *in vivo*. It was recently pointed out in a review of the structure and connectivity of cells and tissues *in vivo*, that cell-cell and cell-ECM connections are continuous in many tissues and that cell mutations or injury alter the connectivity of these connections [16]. The connections are found between ECM and cell surface integrins, cell surface integrins and the cell cytoskeleton, cell cytoskeleton and nuclear cytoskeleton, cell membrane-cell membrane junctions, cell membrane channel interactions, and hormone and growth factor receptor behaviors [16]. These physical and chemical connections play a vital role in the ability of cells and tissues to respond to and generate mechanical forces that influence mechanotransduction and pathobiological changes that occur in health and diseases [2]. Therefore, it is important to consider how these interactions affect measurements of mechanical properties of tissues *in vivo* and consider new methods to measure properties noninvasively.

The concept of using resonant frequency measurements became possible after the development of OCT to capture tissue and material images at very high speeds and its applications in Ophthalmology [30]. By capturing images at high speed, we can follow the deformation of a tissue and its different components in real time. Measurement of the frequency of applied deformation under continuous loading conditions maximizes tissue deformation. When tissue dimensions are measured one can calculate an elastic modulus from the changes in the size. By measuring the relaxation of the tissue size at different loading frequencies the viscous loss can also be determined. At high loading frequencies the tissues act as almost purely elastic materials since relaxation and rearrangement of the cells, water, and other components of the tissue are "frozen" in place.

The ability to noninvasively measure the elastic and viscous behavior of cells, tissues, and implant materials is an important aspect of understanding development, growth, and maturation as well as diagnosing changes that occur during aging and disease. Normal cells have resonant frequencies that are about 50 to 60 Hz and can dissipate large amounts of energy at low frequencies. This allows cells to protect components from mechanical injury at these frequencies. At higher frequencies soft tissues are highly vulnerable to injury especially in older individuals who have reduced numbers of cells and proteoglycan molecules in their tissues. Collagen fibers in skin protect tissues from mechanical damage above 50 Hz but they are less effective since they do not dissipate much energy at their resonant frequencies. In cancerous skin and after tissue injury, cell mutations and deposition of fibrotic tissues stiffen tissues [23]-[25] [29] and do not mechanically protect tissues effectively from injury or provide for normal functioning.

Using VOCT and OCT images the elastic and viscous behavior of tissues can be assessed both *in vitro* and *in vivo* based on measurement of the resonant frequency of cells and tissues. Cells have elastic moduli of about 50% of the dermal collagen in skin and cornea, respectively. All soft tissues have resonant frequencies characteristic of the macromolecular components that make up these tissues. The resonant frequencies and moduli of cells and tissue range from about 50Hz for cells to almost 1000Hz for bone as listed in **Table 1**.

5. Limitations of VOCT

As with all other techniques used to measure the mechanical properties of cells and tissues, VOCT has its limitations. The first limitation involves assuming that the density of the cells and tissues are about 1.0 gm/cc. For materials other than collagenous tissues where the water content is less than about 50% equation (1) needs to be modified as is done for the synthetic polymers. The next limitation is that the strain *in vivo* or *in vitro* needs to be less than the strain in the nonlinear region observed in the tensile stress-strain curve. For some fibrotic tissues and diseases, stress-strain curves in tension need to be measured to confirm equation (1). Finally, the acoustic forces applied need to result in pure tissue compression to create a transverse deformation of the surface of the tissue. Any shear defor-

mation will change the net deformation of the surface. While the frequency of deformation is known from the applied sound waves during VOCT, the exact strain and strain-rate is unknown since each tissue layer will deform a different amount depending on the modulus of each layer.

6. Conclusion

VOCT can be used to measure the elastic and viscous properties of cells, tissues, and implant materials both *in vitro* and *in vivo*. The stiffness of isolated cells is likely to be much smaller than that of cells in series with other cells and collagen *in vivo*. The loss modulus at low strains of cells and tissues *in vivo* is strain rate dependent and decreases with increased strain rates until a strain rate of about 100 cycles/sec is reached. The high viscous component of the mechanical behavior of soft tissues is responsible for dissipating energy applied to soft tissues thereby preventing premature mechanical failure. Changes in elastic moduli of cells, blood vessels, and fibrous tissues can be followed noninvasively *in vivo* to monitor changes in patient health.

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Conflicts of Interest

Fred Silver is a founder of the company that is developing VOCT.

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