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Use of Vibrational Optical Coherence Tomography in Dermatology

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Abstract

In 2014, an estimated 5 million people were treated for skin cancer with a cost of 8.1 billion dollars. While most dermatologists can identify different skin lesions visually, they can't identify the lesion depth or margins without performing a surgical excision and waiting for frozen marginal biopsies. Increased tissue stiffness (also termed modulus) has been shown to be a characteristic of potential tumor metastasis and is characterized by the abnormal deposition of collagen fibers, the major component of extracellular matrix (ECM). This leads to altered tissue mechanical properties of skin.

We have developed a technique to combine optical coherence tomography (OCT) imaging with vibrational analysis (VOCT) to image and to analyze the physical properties of tissues non-invasively and non-destructively. Using images generated by OCT and maps of the modulus as a function of position, we show that it is possible to determine the margins of lesions. Although lesion margins can be marked with VOCT, it is important that a new generation of OCT instruments be developed to more accurately measure lesion depths. Lesion depth analysis would give the Mohs surgeon a better understanding of the extent of the lesion and assist in planning for surgical excision.

In this paper we introduce the use of vibrational optical coherence tomography as a new tool available to non-invasive and non-destructively evaluate skin lesions in the clinic.

Keywords: *Collagen, elastic tissue, fat, lesion margins, cancer, vibrational optical coherence tomography. optical coherence tomography, resonant frequency.*

Introduction

In 2014, an estimated 5 million people were treated for skin cancer with a cost of 8.1 billion dollars [1]. From 1996 until 2013 Mohs surgical procedures to remove skin cancers increased 469% [1]. Basal cell and squamous cell carcinomas affect more than 1 million individuals in the US each year while diagnosis of non-melanoma skin cancer accounts for about 3.5 million new cases in the US each year [1]. Increased tissue stiffness (also termed modulus) has been shown to be a characteristic of potential tumor metastasis [2] and is characterized by the abnormal deposition of collagen fibers, the major component of extracellular matrix (ECM). This leads to altered tissue mechanical properties of skin. While most dermatologists can identify different lesions visually, they can't identify the lesion depth or margins without performing a surgical excision and waiting for frozen marginal biopsies. The time between surgical excision and the pathologic results may be as great as 60 minutes during which time the patients await verification of complete lesion excision before wound closure. The preoperative clinical assessment of the extent of a tumor in three dimensions would facilitate surgical planning and allow dermatologists to know which tumors are deep enough to require a referral to a specialist like a plastic surgeon. With improved

preoperative imaging and measurement of tissue properties, the Mohs micrographic surgery could be shortened, made more cost effective and be less time consuming for patients.

OCT is a non-invasive, non-destructive optical technique for imaging tissue. It has a penetration depth of between 0.5 and 2 mm depending on the light source used and the manner in which the reflected light is analyzed. It has been used to: detect and diagnose non-melanoma skin cancer [3], visualize the functional microvasculature of the skin [4], evaluate the oxidative effects of hair dying [5], determine the margins of basal cell carcinomas before micrographic surgery [6], and map vascularization in plaque psoriasis [7]. Quantitative uses of OCT include measurement of the surface distance to the first vessels [8], characterization of cutaneous wounds [9], thickness measurements in basal cell carcinoma and malignant melanoma [10], differentiation of benign and malignant melanoma [10, 11], and OCT capillaroscopy of nail folds [12]. Besides evaluation of skin lesion pathology, OCT has potential uses in following biofilm formation in skin wounds.

We have developed a technique to combine OCT imaging with vibrational analysis to image and to analyze the physical properties of tissues non-invasively and non-destructively [13-20]. These measurements along with *in vitro* calibration data can be used to interpret mechanical measurements made *in vivo* [13-20]. This technique involves applying a sinusoidal sound wave to a sample at different frequencies and measurement of the frequency at which the maximum tissue displacement occurs [13-20]. The resonant frequency of a material is defined as the frequency at which the maximum displacement is observed [13-20]. Once the resonant frequency is determined, the modulus (also termed stiffness) can be calculated from a calibration curve using the relationship between modulus, the observed tissue thickness, and the resonant frequency [15, 16]. For multi-component tissues such as skin, the resonant frequency of each macromolecular component can be measured and compared to standard calibration curves for different materials [15, 16]. We have reported that the modulus measured at the resonant frequency is almost purely elastic [21] while at lower frequencies the viscous contribution to the modulus can be as high as 25% [21]. The purpose of this paper is to review use of vibrational OCT to image skin to identify the margins of skin lesions and the modulus of different skin components.

Tissue Fibrosis and Collagen Organization

The ability to detect changes in the properties of tissues non-invasively and nondestructively is an important goal of clinicians in order to identify cancerous tissues before they metastasize. Several publications underscore the relationship between cancer and tissue fibrosis [2, 22]. Tissue fibrosis and scarring are characterized by the abnormal deposition of collagen fibers, the major component of extracellular matrix (ECM). This leads to altered tissue mechanical properties [23] and increased tissue modulus and has also been shown to be a characteristic of potential tumor metastasis [2, 22]. A technique to non-invasively image and measure of the mechanical properties of tissues will enable early diagnosis of some of these conditions [13-20].

There have been numerous approaches to image and measure the mechanical propertiesof skin that have been reported in the literature [13]. Most of these techniques fail to measure modulus values that are comparable to values reported using destructive techniques[13]. With the advent of OCT and the use of vibrational analysis it is now possible to measure modulus values of tissues non-invasively that agree with values measured using invasive methods [13-20].

Measurement of Mechanical Properties of Skin

The modulus values of normal and pathologic tissues using invasive techniques has received much attention since the 1970s [24. 25]. We have published several papers on *in vitro* studies of mechanical properties of skin, scar and decellularized human dermis [13-20]. Many of these studies have been conducted with invasive techniques such as Instron testing. Other non-invasive studies have been used to estimate the modulus of tissues; however, the use of these techniques to estimate the stiffness requires a number of assumptions that limit interpretation of the results [13]. As a result of studies, on polymer viscoelasticity, and the introduction of optical coherence tomography in 1996, we have been able to develop a patent pending technique that combines imaging with near infra-red light (OCT) with measuring the tissue resonant frequency by applying sound waves to the tissue at frequencies between 30 and 700 Hz [13-20].

Vibrational Oct (VOCT)

VOCT combines OCT imaging with vibrational analysis to image and to analyze the physical properties of tissues non-invasively and non-destructively [13-20]. What is measured, beside an image of the surface of a material, is the displacement of the tissue as a function of the applied frequency of sound. The resonant frequency is defined as the frequency at which the maximum displacement of the tissue is observed (see Figure 1).

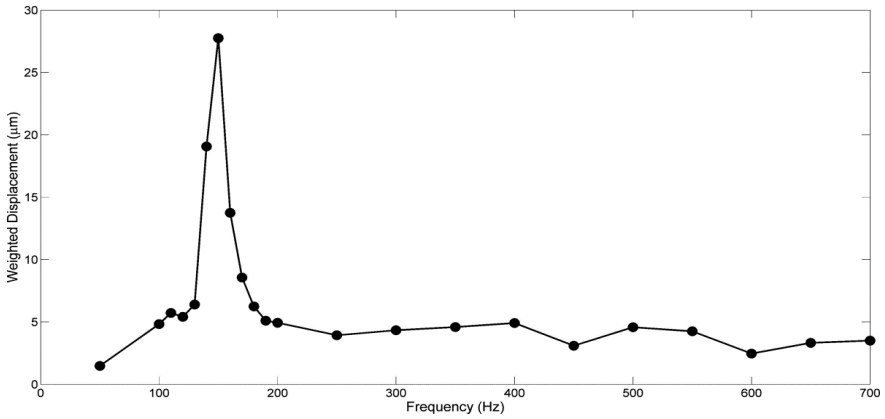

Figure 1. *Plot of weighted displacement versus frequency*

This figure shows the displacement of the tissue as a function of the applied sinusoidal wavelength used to determine the resonant frequency. The sample is vibrated by a speaker at wavelengths between 30 and 700 Hz and the frequency where the maximum displacement is observed is defined as the resonant frequency. The resonant frequency of the collagen sample shown is about 160 Hz.

The resonant frequency squared is related to the tissue modulus *in vitro* using equation (1). *In vivo* the modulus is calculated using equation (2) for tissue with thickness T [15]. The purpose of studying tissues *in vitro* is to set up a calibration curve showing the relationship between tensile testing, which is invasive, and vibrational OCT which is non-invasive.

$$E = m(2\pi f_n)^2\left(\frac{L}{A}\right) \qquad (1)$$

The modulus, E, from *in vitro* vibrational studies on calibration materials, and fat is determined using equation (1) where f_n, *m*, *L* and *A* are the resonant frequency sample mass, length and cross-sectional area, respectively [13-20]. *In vivo* the modulus is determined from equation (2).

$$E=0.034\, f_n^{2.2}/T \qquad (2)$$

These measurements along with *in vitro* calibration data can be used to interpret mechanical measurements made *in vivo* [13-20]. Once the resonant frequency is determined, the modulus can be calculated from a calibration curve (see Figure 2) using the relationship between modulus, the observed tissue thickness and the resonant frequency. For multi-component tissues such as skin, the resonant frequency of each component can be measured simultaneously [12-19].

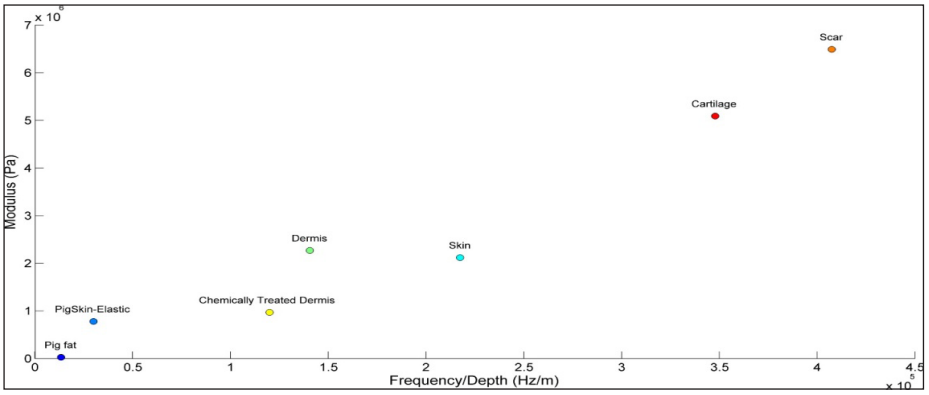

Figure 2. *Calibration curve of modulus versus resonant frequency divided by the sample thickness for skin components.*

The resonant frequency for skin components was determined by vibrating the samples at frequencies between 30 and 700 HZ and the frequency at which the maximum displacement was observed was determined as shown in Figure 1. The sample thickness was determined from measurements made from the OCT images. The modulus is obtained knowing the resonant frequency and the sample thickness. This figure was modified from references [15, 16].

The OCT image of the tissue is obtained by comparing a coherent beam of infra-red light that bounces off the sample with light that does not hit the sample. The phase difference between the reflected and original beams of light is used to create an image and the Fourier transform of the phase difference can be used to measure the displacement.

In order for VOCT to give an image depth of a skin lesion of up to 4.0 mm new technology must be developed since most commercial instruments have a depth of penetration of between 1 and 2 mm. A deep-tissue OCT which will image to depths as great as 4 mm. would provide more accurate lesion depth images required to be useful in Mohs surgery since facial skin is at least 5 mm in thickness.

One advantage of VOCT technology is that the modulus measured at the resonant frequency is an elastic value and is not time dependent. This makes the modulus measured with VOCT a materials property as opposed to Young's modulus which is dependent on the rate of testing. It is important to be able to measure the elastic modulus with VOCT since this will not depend on the rate of deformation.

VOCT has been extended to image and measure the mechanical properties of human skin and scar *in vivo*. An experiment was conducted to determine whether the margins of scar could be determined as well as the scar images [15, 16]. A photographic image of human skin and scar studied is shown in Figure 3 and the OCT images of skin and scar tissue are shown in Figure 4. Photographic images show that the scar was approximately 7 mm in diameter and is clearly demarcated from the surrounding skin by differences in pigmentation. The normal skin appeared to have surface hills and valleys while the scar tissue appeared smoother and showed no papillae.

The plot of weighted displacement versus frequency for scar tissue is shifted to the right as compared to that of normal skin (higher resonant frequency) (Figure 5). The resonant frequency of normal skin was found to be 100 Hz while that of scar tissue was 220 Hz. The edges of the scar had resonant frequencies of both normal skin (90-100 Hz) and scar tissue (220-230 Hz) as shown in Figure 5. The data in Figure 2 show that the modulus of each component found in skin is defined by the ratio of the resonant frequency and the sample thickness. The lowest modulus, 0.03 MPa, is that of fat, while elastic tissue has a modulus of about 0.8 MPa [15, 16], decellularized dermis at a strain of 2 % [15, 16] and skin have moduli of about 2 MPa, and scar has a modulus of about 7 MPa.

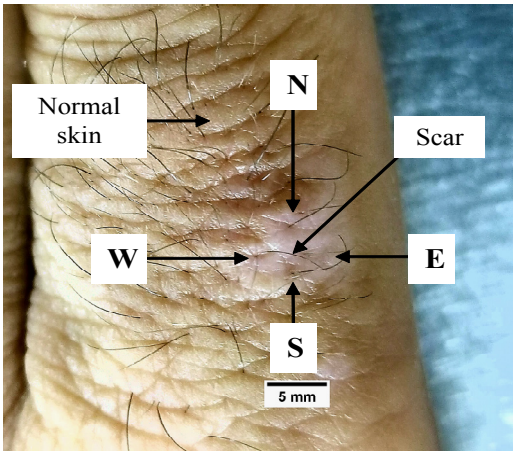

Figure 3. *Photographic image of a skin lesion.*

The skin lesion edges are clearly marked by a change in pigmentation.

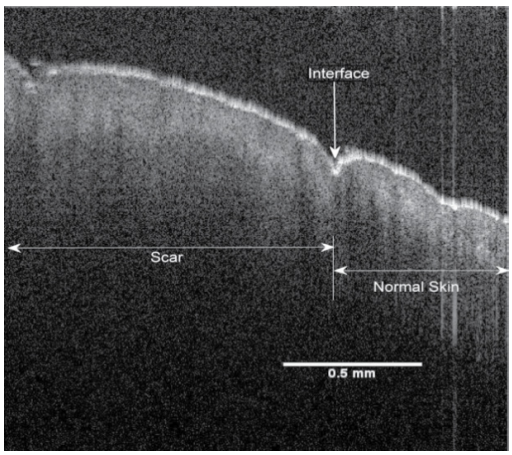

Figure 4. *OCT image of the skin and scar shown in the photograph shown in Figure 3.*

Note the arrow showing the boundary between the normal skin and scar. The scar does not show any papillae when examined in other views of the skin.

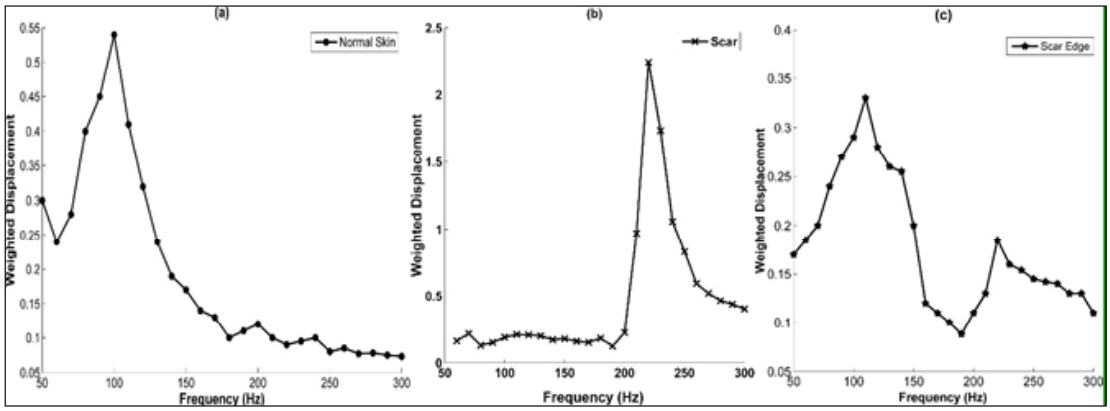

Figure 5. *Weighted displacement versus frequency for the skin (a), scar (b) and skin-scar margin W shown in Figure 3.*

Note the modulus of scar is about 3 times that of normal skin. The interface between skin and scar has resonant frequencies representing both normal skin (90 to 100 Hz) and scar (220 to 230 Hz). This figure was modified from references [15, 16].

Conclusions

Using vibrational analysis and OCT imaging, measurements of the resonant frequency and thickness, can be used to calculate the characteristic moduli of ECM components non-invasively and non-destructively. The numbers generated reflect to a first approximation the elastic moduli and do not depend on measurement of other parameters such as how the volume changes on stretching and material viscoelasticity. Differences in the collagen orientation between skin and scar appear to alter the modulus of the collagen network by a factor of about 3, while the elastic moduli of fat and elastic tissue are much lower than that of collagen networks in skin and scar tissue. Using images generated by OCT and maps of the modulus as a function of position, it should be possible to determine the margins of cellular lesions. such as basal cell and squamous cell carcinomas (cellular lesions would be found on the left in Figure 2) and fibrous lesions such as malignant melanoma (fibrous lesions would be on the right in Figure 2). Measurement of tissue stiffness non-invasively and non-destructively using VOCT suggests that this technique may be useful for the early diagnosis of skin cancers.

Although lesion margins can be marked with VOCT, it is important that a new generation of OCT instruments be developed so that lesion depths can be identified accurately. Better lesion depth analysis would give the Mohs surgeon an indepth understanding of the lesion nature and assist in planning for surgical excision.

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