Characterization of Mammary Tumors Using Noninvasive Tactile and Hyperspectral Sensors

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*Abstract*— **The use of both tactile and hyperspectral imaging sensors, which exploit the mechanical and physiological changes in tissues, can significantly increase the performance in automatic identification of tumors with malignant histopathology. Tactile imaging measures the elastic modulus of a tumor while hyperspectral imaging detects important biochemical markers. Spontaneous mammary tumors in canines were used to demonstrate the efficacy of our approach. The tactile sensor achieved a sensitivity of 50% and a specificity of 100% in identifying malignant tumors. The sensitivity and specificity of the hyperspectral sensor were 71% and 76%, respectively. We investigated several machine learning techniques for fusing the tactile and the spectral data, which increased the sensitivity and specificity to 86% and 97%, respectively. Our tactile and hyperspectral imaging sensors are noninvasive and harmless (no ionized radiation is used). These imaging sensors may not only eliminate unnecessary surgeries, but will also motivate the development of similar sensors for human clinical use, due to the fact that canine and human tumors have similar physiology and biology.**

*Index Terms*—Hyperspectral sensors, tactile sensors, tumors, biomedical imaging, spectroscopy, machine learning.

# INTRODUCTION

B

reast cancer is the second-most commonly diagnosed cancer in American women [1], with approximately 1 in 8 women in the U.S. being diagnosed with breast cancer in their lifetime [2]. Biopsy is the gold standard for diagnosis of cancer. However, it is invasive, time-consuming and requires a trained pathologist. Also in a biopsy, the entire tumor is not evaluated; only a few representative sections are analyzed, which may result in sampling error.

Several other techniques such as mammography (MG), Computed Tomography (CT) and ultrasound (US) are used for tumor detection [3], [4], [5]. MG exposes patients to potentially harmful radiation, requires a trained operator and is expensive. US suffers from the disadvantage of having low image contrast. CT is also expensive and uses high doses of radiation. Since most of these methods are costly and require trained operators, patient access to these important life-saving measures is limited. The long-term goal of this project is to develop a simple-to-use, noninvasive, and risk-free prescreening device that will provide early and affordable detection of potentially life threatening malignant tumors.

Extensive experimental studies on human patients can be both complicated and challenging due to detailed U.S. Food and Drug Administration (FDA) requirements and IRB (Institutional Review Board) approval. Such studies are costly and funding for such research can be difficult to obtain. Spontaneous tumors in companion dogs have similar histopathology and biological behavior as many of the common tumors diagnosed in humans [6] and can provide a unique resource for testing new imaging technology.

Among domestic species, canines have the highest occurrence of mammary cancer. The rate of occurrence is three times that of humans [7]. Mammary cancer in canines has many similarities with breast cancer in women including biology, hormone association, histological appearance and risk factors. Mammary tumors in canines have a wide range of biological behaviors. There are currently no available imaging methods to accurately differentiate between malignant and benign tumors pre-surgery. Therefore, surgical excision and histopathological examination of the tumors remain the standard of care in all canines with mammary tumors.

These canines therefore provide an excellent opportunity to test the tactile and hyperspectral imaging sensors pre-surgery and to correlate the results with the histopathological diagnosis. If found to be accurate, this technology can provide veterinarians with a noninvasive imaging method to determine whether surgery is necessary or monitoring is a reasonable alternative. This is particularly useful in older canines with concurrent health issues. Furthermore, due to physiological similarity between canine and human tumors, this project could motivate the development of similar sensors for human clinical use.

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We have developed a novel and simple-to-use tactile sensor, which quantifies the elastic modulus of tumors. Tactile sensors are used to measure tissue mechanical properties, such as elastic modulus, which vary significantly between normal and cancerous tissue [8]. Cancerous tumors are stiffer and less mobile than normal tissues [8]. Previous tactile imagers, such as the one developed by Sarvazyan and Egorov [9], quantify the size, shape, and hardness of breast lesions based on a pressure sensor array. The tactile imaging sensor (TIS) we have developed uses optical sensors for estimating the mechanical properties of the lesions.

Recently near-infrared (NIR) hyperspectral sensors have been shown to be effective in detecting early mucosal changes at the microstructural, biochemical and molecular levels [10]. Hyperspectral imaging sensors (HIS) have been used to detect prostatic, gastric, and tongue cancer, [11], [12], [13]. In [14], near-infrared reflectance imaging was used to differentiate between an adenocarcinoma and normal tissue in a canine. In this study fluorescence dyes were used, which requires intravenous administration of the compound, resulting in a process that is mildly invasive. Our approach based on a hyperspectral sensor is completely noninvasive.

Overall, the use of hyperspectral imaging for mammary tumor characterization has been limited thus far. We have used a HIS for the in-vivo identification of malignant mammary tumors. Our HIS is coupled with a liquid crystal tunable filter to obtain the differences in spectral properties between malignant and benign lesions. We have used the spectral range *650 – 1100 nm* to quantify the concentration of tissue components such as deoxyhemoglobin, oxyhemoglobin, lipid and water. The concentration of these components changes when a tissue is affected by cancer. Moreover, integration of the two modalities allows measurement of both the biochemical and mechanical properties. The fusion of these two measurements significantly improves our ability to identify malignant tumors.

# Sensor Designs

There are two types of noninvasive sensors employed in this work. Our tactile imaging sensor is an optical imaging technique based on total internal reflection. Hyperspectral imaging sensor operates in the near-infrared spectral region and gives both spectral and spatial information simultaneously. A major goal of this work is to fuse the information provided by these sensors to improve detection performance.

## Tactile Imaging Sensor

The tactile imaging sensor consists of an optical waveguide unit, a light source unit, a high-resolution camera unit, a computer unit, and a force gauge unit as shown in . The optical waveguide unit is made of polydimethylsiloxane (PDMS) which is prepared from component materials RTV 6136-D1 (provided by R. S. Hughes Co., Inc., Sunnyvale, CA, USA). The sensing probe is flexible, transparent and inert. The sensing area is *23 mm × 20 mm*. The camera unit consists of a mono cooled charged-coupled-device (CCD) camera (Guppy F044B-NIR, Allied Vision Technology GmbH, Stadtroda, Germany). The pixel resolution of the sensor is *8.6 μm × 8.3 μm*. The camera communicates with the computer unit via an IEEE 1394A (Firewire) interface.



Fig. 1. In TIS, the internally reflected light inside the optical waveguide scatters when the waveguide is compressed with an inclusion. The scattered light is captured by the CCD camera.

Between the camera and the silicon probe, a heat resistant borosilicate glass is added to provide structural support. The light source unit consists of four ultra-bright white light emitting diodes (LED). The luminous intensity of each LED is *1500 mcd*. The applied force on the waveguide is detected using a force gauge (Mark-10 Corporation, Copiague, NY, USA). The range and the resolution of the force gauge are *0* to *50 N* and *1.0 × 10−3 N* respectively.

The air that surrounds the optical waveguide has a lower refractive index than that of the waveguide [15]. Because of Snell’s law and the principle of total internal reflection (TIR), the light that is incident onto the waveguide is trapped inside the waveguide. In the current design, the light is illuminated over the critical angle for the complete reflection of the light within the waveguide. When the waveguide is compressed by an object, the contact area of the waveguide deforms, which causes the light to scatter. The scattered light is captured by a charge coupled device (CCD) camera, as shown in Fig. 1.

## Hyperspectral Imaging Sensor

Our portable hyperspectral tunable imaging sensor, shown in Fig. 2, consists of a digital imager (QImaging Inc., Surrey, BC, Canada), a liquid crystal tunable filter (Cambridge Research & Instrumentation Inc., Woburn, MA, USA), and a controller. The digital imager is a mono-cooled charge coupled device. It has a cell size of *6.45 μm* (V) *×* *6.45 μm* (H) and *12-bit* output. The range of wavelength of the filter is *650 – 1100 nm* in increments of *10 nm*. The function of the controller is to synchronize the CCD camera and the filter. Dual *500 W* quartz tungsten halogen lamps were used for illumination while acquiring the images. Visualization of images and analysis of the spectral data were performed using ENVI v4.5 (Exelis Visual Information Solutions, Boulder, CO, USA) and The Unscrambler® v10.1 (CAMO Software AS, Oslo, Norway). The total scanning time of the controller is 25 seconds.

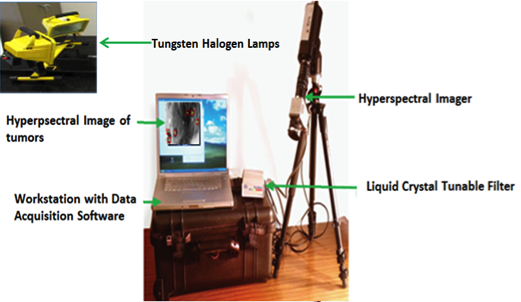


Fig. 2. A schematic view of the hyperspectral imaging acquisition system, which consists of a digital imager, a tunable filter and a controller, is shown.

During hyperspectral imaging, the data produced by the sensor consists of a collection of images as shown in . The set of images can be represented by a three-dimensional cube where the first two coordinates represent the spatial coordinate of a pixel and the third coordinate gives the wavelength of a particular spectral band. The data size of one image is approximately 197 MB.

# image processing algorithms

Post-processing of the TIS and HIS data is critical to achieving good classification performance. In this section, we discuss the signal processing and machine learning algorithms applied to this data, and how we fuse the outputs to improve performance.

## Tactile Image Processing

TIS data is used to solve for the elasticity of the lesion by estimating the diameter and depth of the lesion. A simple threshold for the amplitude value of a pixel is used to reject background noise. This amplitude threshold was determined experimentally to be 20 (the maximum value of an *8-bit* pixel is *255*). A scale factor of *6.79×10-3 mm/pixel* was used to convert pixel distances to absolute distances. This scale factor was also determined experimentally.

Assuming the tissue inclusion is spherical, the pixel values will be normally distributed [16]. The *x* and *y* coordinates of the centroid are calculated as follows:

 ,, (1)

(2)

where *I(x,y)* represents the pixel intensity. The pixel value at the centroid is used for relative depth estimation, and *d* signifies the centroid coordinates.

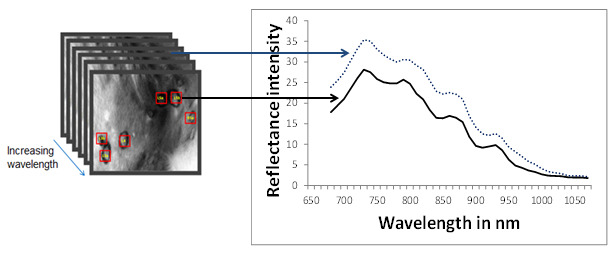


Fig. 3. A schematic view of the hyperspectral image of the tumors from a canine patient is shown, along with reflectance measurements for a benign (dotted line) and malignant tumor (solid line).

Young’s modulus is commonly used to estimate the elasticity of an elastic isotropic material. Here, to calculate the Young’s modulus of the lesion, we first estimate the normal vertical force. The formula of the normal force was found by experimental calibration. Using a force gauge, the waveguide was compressed at different forces and a linear relationship between the normal force and the integrated pixel values was found [16]. Using the slope of the best fit line, the normal force was found to be the following:

, (3)

where *Vf* is the normalized vertical force and *Spixel* is the summation of pixel intensity values in a tactile image.

Once we obtain the vertical force for both images, we calculate the tensile stress for both images using:

 . (4)

The contact area (*A*) is taken to be the area of the sensor probe, since in most applications the tumor is larger than the sensor. We then divide by *1000* to convert *mN/mm2* into *N/m2*.

The strain is determined by taking the change in depth divided by the original depth. After calculating the tensile strain, we solve for Young’s modulus, *E*:

 . (5)

A higher value of Young’s modulus indicates there is a greater probability that the tumor is malignant [8].

## Hyperspectral Image Processing

The reflectance spectral data were smoothed using a Savitzky-Golay filter [17] with a 2nd - order polynomial and a *70 nm* analysis window. These smoothed values were post-processed using quantile normalization [18].

To differentiate between malignant and benign breast lesions, a tissue optical index (TOI) was calculated [19]:

. (6)

A higher total hemoglobin content (the sum of deoxy- and oxyhemoglobin) [HbT] indicates higher tissue blood volume and malignancy. Higher water content [H2O] suggests abnormal accumulation of interstitial fluid in the tissue which indicates malignancy. Decreased lipid content [Lipid] suggests that the parenchymal adipose tissue has been displaced which is a warning sign for cancer. These changes can be grouped together to enhance contrast through the formation of the TOI, where elevated TOI values suggest high metabolic activity and malignancy [19].

Since we do not have concentration information of the chromophores (water, hemoglobin, and lipid), we rewrite the TOI formula in terms of reflectance intensity. The model used for calculating the TOI values is:

, (7)

where *R* signifies the reflectance value of the particular chromophore. A decrease in reflectance intensity is observed with an increase in hemoglobin and water concentration [20]. An increase in reflectance intensity correlates with an increase in lipid concentration [21]. Since the model in (7) is in terms of reflectance values, the lower the *TOI*, the higher the probability of a malignant tumor.

## Fusion Using Machine Learning

The tactile and hyperspectral imaging results were fused using machine learning to optimize the mapping between the observations (tactile and spectral data) and the characterization (malignant or benign). We used a set of data points with known labels as training and a held-out set for evaluation. Because there was a limited amount of data available, we have used a leave-one-out cross-validation approach [22]. We applied three classification algorithms: Support Vector Machines (SVM) [23], K-Nearest-Neighbor (KNN) [24], and Random Forests (RF) [25]. All algorithms were based on publicly available implementations in MATLAB.

SVMs have been successfully used for NIR spectroscopic applications [26], [27], [28]. In these experiments we used SVMs with two kernels: Radial Basis Functions (RBF) and polynomial functions [29]. We tuned the kernels using leave-one-out cross validation since the sample size was small.

KNNs have been successfully applied to a wide range of pattern recognition applications and remain an important baseline approach. Recently, KNN has been shown to be successful at classifying hyperspectral data [30], [31]. The KNN distance metrics used in this paper are the Euclidean and Chebyshev metrics [32]. The feature vectors were normalized to have a zero mean and a unit variance before application of the classification algorithm.

RF is a very powerful general purpose classification method that is robust to noise, elegantly avoid overfitting and computationally fast [25]. RFs operate by constructing a large number of decision trees for the training set. RFs output the class which is the mode of the classes output by the individual trees. RFs have previously been found to be useful for regression studies in order to model spectroscopic data [33]. A detailed treatment of RFs can be found in [25].

Sensitivity and specificity were used as statistical measures for comparing the performance of the algorithms. Sensitivity is the ability of an algorithm to correctly predict that a tumor is malignant. Specificity is the ability of the algorithm to correctly predict that a tumor is benign.

# clinical experiments

Temple University and the University of Pennsylvania Veterinary Hospital collaborated on the collection of tactile and hyperspectral data from canine patients. We refer to this dataset as the TU-UP Corpus. The animal experiments were approved by the University of Pennsylvania Institutional Animal Care and Use Committee (IACUS) Protocol #803829. During image acquisition, veterinarians held the canine in a stationary supine position by gentle manual restraint, as shown in . The tumors were marked with a black marker, as shown on the right in , so that identification of the tumors would be easier during image analysis. After imaging was complete, the canines underwent surgical excision of all tumors. The tumors were submitted for biopsy. The biopsy results were compared with our image analysis results.

A total of *22* tumors (*7* malignant and *15* benign) across nine canines were investigated using hyperspectral imaging. Regions of interest (*ROI*) were defined for each tumor as the entire tumor area. Using the same hyperspectral image analysis, we also collected *ROIs* of the normal tissue adjacent to the tumors, using approximately the same pixel size as was used for the tumor tissue. There were *22* *ROIs* of normal tissue across the nine canines. For the tactile experiment, we obtained tactile data for 21 tumors (6 malignant and *15* benign). While fusing the tactile and hyperspectral data, we replaced the missing data points with an average of all values in the dataset.

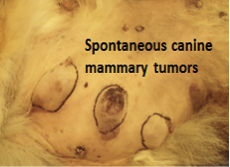
 

Fig. 4. On the left, a veterinarian holds a canine in a supine position during image acquisition. On the right, spontaneous canine mammary tumors are marked with a black marker for easier identification of tumors during image analysis.

## Tactile Imaging Results

Young’s Modulus, *E*, was calculated for each of the 21 tumors using the TIS. The results are shown in , along with the histopathology results. Using a Young’s modulus value of 144.90 as the threshold, the sensitivity and specificity of this method in identifying malignant tumors was 50% and 100%, respectively, and represents our baseline performance for a TIS-only system.

## Hyperspectral Imaging Results

The spectra of the malignant and benign tumors differed significantly as shown in . The reflectance intensity of malignant tumors was lower than that of benign tumors in the range of *650­­­­ – 800 nm*. Chromophore-specific wavelengths were selected by applying second derivative reflectance spectra. Peaks at *700 nm*, *840 nm*, *900 nm* and *970 nm* were observed. These peaks were attributed to deoxyhemoglobin, oxyhemoglobin, lipid and water respectively.

The TOI values were calculated using (7). Malignant tumors had lower TOI values than that of benign tumors. After computing the TOI values, the optimal threshold for tumor classification was calculated using relative operating characteristic curve (ROC). The threshold that gives the best sensitivity and specificity following the method in [34] was chosen using the intersection of the ROC curve and an equal error rate line. This was computed to be 35.65. Using this TOI threshold, we obtained a sensitivity and specificity of 71% and 76% respectively.

## Fused Algorithm Results

We next investigated the use of three machine learning algorithms, RF, SVM and KNN, to fuse the tactile and hyperspectral data. The results are summarized in . For each algorithm, we have tuned a key system parameter to optimize performance. For RF, this parameter was the number of trees. The optimal number of trees was 60, resulting in a sensitivity and specificity of 43% and 100% respectively.

For SVM, two kernels were evaluated: polynomial and radial basis function (RBF). For the polynomial kernel, the key parameter is the order. For RBF, the key parameter is the shape parameter. Performance of the RBF kernel was the same for values of the shape parameter ranging from 1 to 6.

Table 1. The histopathology and Young’s modulus values for the lesions in canine patients are shown.

|  |  |  |
| --- | --- | --- |
| **Tumor** | **Histopathology** | **Young’s Modulus (kPa)** |
| 1 | Adenoma | 2.74 |
| 2 | Carcinoma | 944.36 |
| 3 | Adenoma | 27.39 |
| 4 | Carcinoma | 434.17 |
| 5 | Carcinoma | 3.37 |
| 6 | Plasma Cell Tumor | 27.90 |
| 7 | Carcinoma | 21.65 |
| 8 | Normal Tissue | 18.14 |
| 9 | Benign Mixed Tumor | 46.64 |
| 10 | Benign Mixed Tumor | 19.14 |
| 11 | Benign Mixed Tumor | 60.31 |
| 12 | Normal Tissue | 144.91 |
| 13 | Adenoma | 7.78 |
| 14 | Benign Mixed Tumor | 19.34 |
| 15 | Complex Adenoma | 105.71 |
| 16 | Benign Mixed Tumor | 121.79 |
| 17 | Complex Adenoma | 34.83 |
| 18 | Carcinoma | 424.88 |
| 19 | Adeno-carcinoma | 21.23 |
| 20 | Adenoma | 3.28 |
| 21 | Adenoma | 10.21 |

For KNN, there were two design parameters: the distance measure (Chebyshev vs. Euclidean) and the number of nearest neighbors, *K*. Chebyshev distance measure with K=2, 3, 4 gave the overall best performance. Among all the algorithms, the best sensitivity and specificity (86% and 97%, respectively) was obtained using KNN in the above configuration.

# conclusions

Table 2. The sensitivity and specificity are shown for the TU-UP dataset.

|  |  |  |  |
| --- | --- | --- | --- |
| **Algorithm** | **Parameter** | **Sensitivity (%)** | **Specificity (%)** |
| RF | No. Trees |  | |
| 50 | 43 | 89 |
| 60 | 43 | 100 |
| 70 | 43 | 97 |
| 80 | 43 | 97 |
| 90 | 43 | 95 |
| 100 | 43 | 89 |
| SVM  (poly.) | Order |  | |
| 2 | 57 | 95 |
| 3 | 71 | 92 |
| 4 | 57 | 89 |
| 5 | 57 | 89 |
| SVM (RBF) | Shape |  | |
| 1,2,3,4,5,6 | 57 | 100 |
| KNN ( Cheby.) | K |  | |
| 1 | 57 | 92 |
| 2 | 86 | 97 |
| 3 | 86 | 97 |
| 4 | 86 | 97 |
| 5 | 57 | 92 |
| KNN (Euclid.) | K |  | |
| 1 | 71 | 94 |
| 2 | 71 | 94 |
| 3 | 57 | 91 |
| 4 | 57 | 91 |
| 5 | 42 | 89 |

In this paper, we successfully fused information from hyperspectral and tactile sensors for mammary tumor characterization. We were able to discern malignant tumors in canine patients using the reflectance intensity information from hyperspectral data and the calculated elastic modulus from the tactile data. The reflectance intensity of malignant tumors was lower than benign tumors over the wavelength region of *650 ­­– 800 nm*. This is attributed to increased microvasculature and metabolic activity in malignant tissue, which increases the concentration of deoxyhemoglobin and oxyhemoglobin in tumors that are malignant.

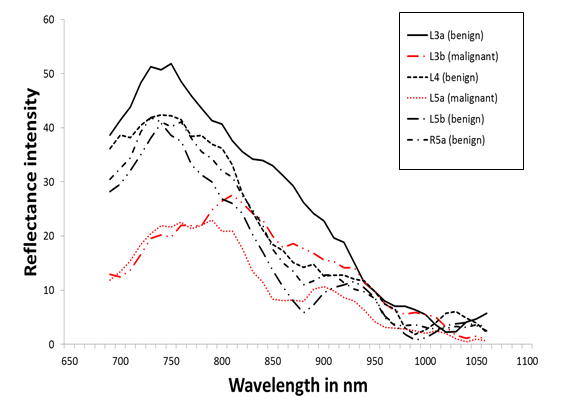


Fig. 5. The reflectance spectra are shown for a patient that had 2 malignant and 6 benign tumors. The malignant tumors have lower reflectance intensities than the benign tumors in the normal regions in the wavelength range of *650 – 800* *nm*, which indicates increased absorption in this region.

Note that there was a variation in skin coloration for the canine patients included in this study, yet the TOI method was still effective. Since the calculation of the TOI involved the ratio of the reflectance intensity at specific wavelengths, it reduced any effect that the skin color might have. A more comprehensive dataset is needed to be able to generalize these results to a larger population of canines.

Fusing tactile and hyperspectral imaging sensors increased performance significantly. Preliminary results with 22 canine mammary tumors showed that the sensitivity and specificity of the tactile imaging sensing method was 50% and 100% respectively. The sensitivity and specificity of the hyperspectral imaging sensor was 71% and 76% respectively. We have demonstrated that fusing the tactile and hyperspectral data with the KNN algorithm improved sensitivity and specificity to 86% and 97% respectively. We would expect that if the dataset were much larger, the difference between these algorithms would reduce, since SVM and RF typically need much larger datasets to be effective and KNN is asymptotically optimal.

Since the dataset being used currently is collected primarily for surface tumors, the reflectance value recorded by the hyperspectral imaging system is directly used as the reflectance value of the tumor without adjusting for any aberrations resulting from skin depth. These aberrations can possibly induce an error in the device recorded reflectance value in skin-deep tumor detection. In the future, we can use the image of the resected tumor cells after biopsy for an *in-vitro* spectral imaging study; measure the depth of the overlaying skin and the compare the difference in the reflectance values to study the role of skin depth in these results.

The tactile sensor requires an ambient environment that is relatively dark since the tactile sensor is based on the detection of scattered light from the PDMS probe. Therefore, the intensity of the background light should be lower than the intensity of the LEDs in the tactile sensor.

In the future, we plan to collect more canine spectral and tactile data so that we can generalize the predictions put forward in this study. To have a 95% confidence that the difference in error is statistically significant, we need to triple the size of the database to approximately 120 samples. The temperature of the tungsten halogen lights used for the hyperspectral sensor was very high, thereby making it uncomfortable for the patients. In future, we plan to use fiber optic cabling to deliver the light to the sample. That should result in a decrease of the temperature of the lights, as well as make the hyperspectral experimental setup more flexible. It would also result in uniformity of the incident light. Another improvement that we plan to implement is to design the algorithms that would give us results in real-time. This would help surgeons identify tumor margin during a surgery.

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