Cancer Detection Probe Combining Raman and Resonance Sensor Technology – Experimental Study on Temperature Dependence and Effects of Molding

M. Nyberg[1,2], K. Ramser[1,2], and O.A. Lindahl[1,2]

[1] Department of Computer Science and Electrical Engineering, Luleå University of Technology, Luleå, Sweden
[2] Centre for Biomedical Engineering and Physics, Luleå University of Technology and Umeå University, Luleå and Umeå, Sweden

Abstract— **Prostate cancer is a major health problem among men in Europe and the USA. Tactile resonance technology and Raman spectroscopy have both shown promising results *in vitro*, detecting and diagnosing cancer tumors respectively. A new approach, combining the strength of resonance technology and Raman spectroscopy is investigated. This study deals with the effects of molding a Raman fiber optic probe into a cylindrical resonance sensor element (RSE) to achieve a combined probe. Heat induced by the Raman spectroscopy laser might affect temperature dependent properties of the RSE. Also, molding a Raman probe into a RSE will affect its properties. The RSE temperature dependency was investigated using the resonance sensor system Venustron®. The Raman fiber optic probe was simulated by a thin steel pipe which was molded into a single cylindrical RSE. The effects on the frequency characteristics when modifying the RSE were investigated with a network analyzer.**

Although the resonance frequency of a RSE is temperature dependent, the frequency shift, as used for calculating stiffness, is not noticeably affected by moderate temperature variations. The RSE properties change less by using a small amount of filler material and a small diameter of the Raman probe.

Keywords— **Prostate cancer, Raman spectroscopy, tactile resonance, resonance frequency, frequency shift.**

I. INTRODUCTION

Prostate cancer is a major health issue among men in Europe and the USA [1] and many new detection methods are investigated. One area of research is to complement the subjective method of palpation for detecting prostate cancer tumors with an objective method based on resonance sensor technology [2, 3]. Another is to complement visual histological analysis with a biochemical analysis using Raman spectroscopy [4]. The resonance sensor element (RSE) is an essential part of an instrument based on a tactile resonance sensor. The RSE is a piezoelectric ceramic which is set to oscillate by applying a sinusoidal electric potential. The RSE resonance frequency changes when the sensor is attached to an object. The frequency change is dependent on the acoustic impedance of the objects [2].

Resonance sensor technology is used within the field of medicine to detect liver fibrosis [5], pulmonary tumor nodules [6], breast cancer lesions [7], and as a cancer indicator concerning lymph nodes [8].

Recent studies have shown that resonance sensors are able to indicate volumes with high risk of tumors by localizing stiff volumes within the tissue [2,9]. However, it has limited capabilities to discern healthy and cancerous stiff tissues [9].

Raman spectroscopy is an optical method. A monochromatic laser beam is guided by an optical fiber and illuminates the sample. Light is inelastically scattered by the molecules in the sample, causing a shift in the wavelength. The spectrum of the back-scattered light reveals the molecular contents of the sample. Raman spectroscopy is able to discern tissue types on a molecular basis [4]. Concerns about laser induced tissue damage prevent this technique to be used unrestrained.

Near infrared Raman spectroscopy makes use of a laser in the near infrared region. That can induce heating of the sample and its surrounding. The RSE resonance frequency is temperature dependent and any temperature change induced by the laser might have an effect on the resonance sensor [10]. Also, the frequency response of the RSE is likely to change as the Raman probe is molded into the RSE, as the acoustic impedance is changed by adding material to the sensor element.

The overall aim is to develop a medical instrument, combining near infrared Raman spectroscopy and resonance sensor technology, with which it would be possible to detect and diagnose cancerous tumors in near real-time.

The aim of this study was to investigate what effects molding a Raman probe into a cylindrical RSE have on the resonance properties of the RSE; and how the RSE properties responds to temperature variations.

II. MATERIALS AND METHODS

A. Molding a Raman probe into a resonance sensor element

The Raman spectroscopy probe consists of a thin steel pipe holding a set of optical fibers. Therefore, the Raman probe was substituted by a thin steel pipe during this experiment. Piezoelectric ceramics can be found in various shapes and by choosing a cylindrical RSE, the steel pipe could be positioned at the center of the sensor. The RSE

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was successfully molded to a force transducer by using rubber latex to build a functional instrument by Eklund *et al.* [11] and Hallberg *et al.* [12]. Each of two steel pipes (Ø 0.8 mm and Ø 1.2 mm) was molded into a cylindrical RSE (Length 15 mm, $Ø_{outer}$ 5 mm, $Ø_{inner}$ 2.8 mm, PZT-ceramic, Morgan Electro Ceramics, Bedford, OH, USA) using rubber latex (Wacker Elastosil RT622, Wacker Chemie GmbH, München, Germany) as filler material. The steel pipes were molded into the center of a cylindrical RSE in two fashions: Either, the RSE was completely filled with rubber latex, or filled to half its length (Figure 1).

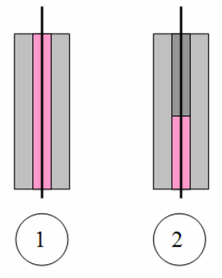

Figure 1 Steel pipes molded into cylindrical RSE with: 1) Full amount of filler material. 2) Half amount of filler material.

The resonance frequency and signal characteristics of the modified RSE were determined by using a network analyzer (Agilent E5100 A 10 kHz – 300 mHz Network Analyzer, Japan), and compared to the unmodified RSE. The frequency was swept in steps of 150 Hz over the interval 95 kHz – 120 kHz, covering both the resonance and anti-resonance frequency peaks for this particular RSE. The shape of the resonance peak was described by its Q-value (Equation 1) where f_r and f_l are the right and left frequencies at half the peak intensity [13].

$$Q = \frac{\sqrt{f_r \times f_l}}{f_r - f_l} \qquad (1)$$

Statistical average (mean ± SD) was calculated for measurements on the unmodified sensor element (Microsoft® Excel®, USA). The parameter values of the molded sensor elements were presented as the difference from the unmodified sensor element.

B. Temperature dependency

Previous studies regarding prostate tissue stiffness have made use of the resonance sensor system Venustron® (Axiom Co. Ltd., Koriyama Fukushima, Japan) [9]. The resonance frequency and frequency shift temperature dependency of a resonance sensor were, therefore, investigated in this study by using this commercially available resonance sensor system. The resonance frequency and frequency shift response were investigated in a clinically acceptable temperature span, i.e. at room temperature and temperatures of body tissue.

The Venustron® resonance sensor consists of: a PZT-element with a hemispherical plastic tip, a force transducer, and a motor to control the sensor tip movement. Measurements were performed on a rubber silicone plate (Ø 85 mm, height 13 mm, Wacker SilGel 612, Wacker-Chemie GmbH, Germany) with penetration value 192 mm x 10^{-1} (DIN ISO 2137, hollow cone 150 g). The rubber silicon plate was powdered with a thin layer of aluminum oxide (Buehler, Lake Bluff, USA) to prevent the sensor tip to stick to the surface. An isolated box (Cardboard box; 21 cm x 29 cm, height 31 cm. Styrofoam insulation inlay; thickness 2 cm) was built around the experimental setup. The ambient temperature of the experimental setup was varied by slowly heating the enclosed air with a field-effect transistor (generic brand, 15 W) mounted to an aluminum cube (1 dm^3). During measurements in room temperature (23°C ± 1.0°C) the temperature of the rubber silicone was varied by either cooling in a refrigerator or heating on top of the aluminum cube. The temperature was monitored using 0.1°C resolution thermometers (TFA Lab Thermometer IP65 models LT-101 and LT-102, PRC TFA Dostmann GmbH & Co. KG Wertheim, Germany) with an air probe positioned at the resonance sensor element and a penetration probe embedded in the rubber silicone plate.

During a Venustron® measurement the parameters; frequency shift, *Δf*, impression depth, *d*, and force exerted on the sensor tip, *F*, were sampled at 200 Hz. The resonance frequency immediately before impression was also recorded. Impression speed was set to 1 mm s^{-1}, and maximum impression depth was set to 1 mm. Statistical average (mean ± SD) was calculated for measurements performed ten times at constant temperature, ±0.05°C, and the resonance frequency temperature dependency was investigated using regression analysis (Microsoft® Excel®, USA). The ambient temperature was varied over a 5.7°C interval (22.7°C – 28.4°C) in steps of 0.5°C. For measurements in normal room temperature (23°C ± 1.0°C), the average temperature of the rubber silicone plate was set to 13.6°C, 22.5°C, 28.5°C, and 36.9°C. The temperature coefficient of the resonance frequency, $|TC\_f_r|$ (ppm/°C), was calculated (Equation 2) with a modification of the IEEE Standard [14], where T is the temperature span and $f_{r[x°C]}$ is the resonance frequency at x°C.

$$|TC - f_r| = \frac{f_{r[28.4^oC]} - f_{r[22.8^oC]}}{T \times f_{r[22.8^oC]}} \qquad (2)$$

The frequency shift temperature dependency was analyzed at chosen impression depths by comparing two measurement setups. Measurements performed at varied ambient temperature and measurements performed at normal room temperature where only the measured objects temperature was varied, respectively.

III. Results

C. *Molding a Raman probe into a resonance sensor*

The resonance frequency of an unmodified sensor element was 114680 Hz ± 67 Hz (n = 5). When the Ø 0.8 mm and the Ø 1.2 mm steel pipe were molded by filling half of the RSE with filler material the resonance frequency dropped by 180 Hz. When the Ø 0.8 mm steel pipe was molded by filling the RSE full of filler material the resonance frequency dropped by 330 Hz, and for the Ø 1.2 mm steel pipe it dropped by 480 Hz (Figure 2a).

The Q-value for an unmodified sensor element was 188 ± 16 (n = 5). When the Ø 0.8 mm steel pipe was molded by filling half of the RSE with filler material the Q-value dropped by 53, and by full filling it dropped by 77. When the Ø 1.2 mm steel pipe was molded by filling the RSE full of filler material Q-value dropped by 66, and by full filling it dropped by 89 (Figure 2b).

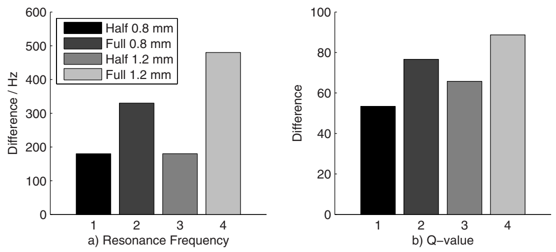

Figure 2 Difference from the unmodified RSE: 1) Half amount of filler material and Ø 0.8 mm steel pipe, 2) full amount of filler material and Ø 0.8 mm steel pipe, 3) half amount of filler material and Ø 1.2 mm steel pipe, 4) full amount of filler material and Ø 1.2 mm steel pipe.

D. *Temperature dependency*

The standard deviation of the base resonance frequency was less than 5 Hz and 0.1°C for the ordinate temperature, except for the refrigerated rubber silicone (SD = 14.4 Hz and 1.3°C).

The resonance frequency had a linear dependency of the ambient temperature in the temperature interval T_{amb} = 22.7°C – 28.4°C ($f_{amb}(T) = 59762 - 36.1T$, $R^2 = 0.991$, n = 7). In that temperature span the temperature coefficient, $|TC\_f_r|$, was 609.5 ppm/°C. Measurements in normal room temperature had a linear dependency of the measured objects temperature in the temperature interval T_{obj} = 13.6°C – 36.9°C ($f_{obj}(T) = 59026 - 4.0T$, $R^2 = 0.995$, n = 4).

As the ambient temperature was varied over a temperature span of 5.7°C, the maximum frequency shift was 2.3 Hz at impression depth 0.1 mm and 20.7 Hz at impression depth 1.0 mm (Figure 3).

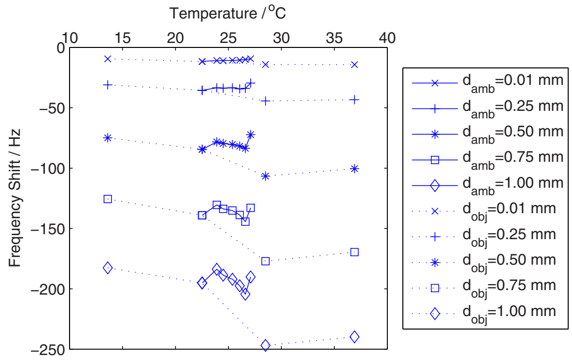

Figure 3 Frequency shift at various impression depths: Straight lines when ambient temperature was varied; dotted lines for varied rubber silicone plate temperature spanning from refrigerated to normal body temperature.

IV. Discussion

This study evaluated effects of molding and temperature dependencies of a RSE. It has taken the integration of a RSE and a Raman probe one step further towards an instrument for prostate cancer detection.

The resonance frequency and Q-value changed in a similar pattern when molding a steel pipe into a cylindrical resonance element. The property values changed more as an increased amount of filler material was used and when the diameter of the steel pipe was larger. The diameter of the steel pipe was less important than the amount of filler material.

Before impression, the resonance frequency did not change due to an addition of material but was solely temperature dependent and was utilized to monitor the resonance sensor element's intrinsic temperature. The RSE resonance frequency was linear to the RSE temperature, $f_{amb}(T)$. The temperature of the rubber silicone plate was varied over a temperature span of 13.6°C when measurements were performed at normal room temperature. The RSE's temperature varied only by 2.65°C during those measurement series, according to $f_{amb}(T)$. The small temperature change of the RSE could be explained by the short time of contact between the RSE and the rubber silicone plate (3 s), compared to the time the RSE was completely surrounded by air of normal room temperature (60 s).

The RSE temperature change was smaller in one measurement setup and larger in the other. If the frequency shift would be temperature dependent, the observed frequency shift should be larger with larger temperature. Since it was not, the frequency shift was not due to the temperature change of the RSE. Instead, the rubber silicone became softer as its temperature increased and the frequency shift increased correspondently. However, the change in frequency shift due to normal room temperature variations, 21 Hz, is less than the standard deviations in frequency shift as reported in previous studies and thus negligible [2, 9, 12, and 15].

Although the resonance frequency of the Venustron® is clearly temperature dependent, the frequency shift is small enough to vanish in the expected standard deviation for measurements performed in normal room temperature. If the time of contact between the RSE and the measured object is kept short, this would hold true even if the measured object is refrigerated or at body temperature.

The Venustron® temperature coefficient of about 600 ppm/°C was relatively large compared to commercially available hard ceramic PZT-RSE's, which temperature coefficients are reported to be less than 100 ppm/°C [14]. However, those RSE's are not manufactured for medical applications; but a less temperature sensitive resonance sensor might be possible to consider for combining with a Raman probe.

V. Conclusions

This study show that when a Raman probe is molded into a cylindrical RSE, less filler material and a small diameter of the Raman probe had less impact on the RSE properties. Therefore, it can be suggested from this study that a Raman probe with a small diameter and a minimum of rubber latex, in contact with the RSE, should be used when building an integrated instrument.

If the RSE temperature of a combined instrument is changed due to heat induced by the Raman laser within 22.7°C – 28.4°C, its ability to detect stiffness would not be affected.

Although this study gave valuable information, further studies must be performed for finding an optimum way of molding a Raman probe into a cylindrical RSE.

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Address of the corresponding author:

Author: Morgan Nyberg
Institute: Department of Computer Science and Electrical Engineering
City: Luleå
Country: Sweden
Email: Morgan.Nyberg@LTU.SE