A Flexible Resonance Sensor System for Detection of Cancer Tissue – Evaluation on Silicone

Anders P Åstrand
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Anders P Åstrand
Dedicated to my son Craig-Björn
Greatly loved and missed
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Abstract

The most common form of cancer among men in Europe and the US is prostate cancer. When a radical prostatectomy has been found necessary, it is of interest to examine the prostate, as tumour tissue on the capsule might indicate that the cancer has metastased. This is commonly done by a microscope-based morphometric investigation. Tumour tissue is normally stiffer than healthy tissue. Sensors based on piezoelectric resonance technology have been introduced into the medical field during the last decade. By studying the change in resonance frequency when a sensor comes into contact with a material, conclusions can be drawn about the material.

A new and flexible measurement system using a piezoelectric resonance sensor has been evaluated. Three translation stages, two for horizontal movements and one for vertical movement, with stepper motors are controlled from a PC. A piezoelectric resonance element and a force sensor are integrated into a sensor head that is mounted on the vertical translation stage. The piezoelectric element is connected to a feed-back circuit and resonating at its resonance frequency until it comes into contact with a material, when a frequency shift can be observed. The force sensor is used to measure the applied force between the sensor and the material. These two parameters are combined into a third, called the stiffness parameter, which is important for stiffness evaluation. For measurements on objects with different geometries, the vertical translation stage can be aimed at a platform for flat objects or a fixture for spherical objects. The vertical translation stage is mounted on a manual rotational stage with which the contact angle between the sensor and the measured surface can be adjusted. The contact angles covered are between $0^\circ$ and $35^\circ$ from a line perpendicular to the surface of the measured object. The measured objects used were made from silicones of different stiffness and in the shape of flat discs and spheres. The indentation velocity of the sensor can be set at 1 mm/s to 5 mm/s. In the three papers that are the base for this licentiate thesis, we have investigated the dependence of the frequency shift, the applied force and the stiffness parameter on the contact angle, and the indentation velocity at different impression depths. The maximum error for the measurement system has also been determined.

The results of the measurements indicate that great care must be taken when aiming the sensor against the surface of the point where the measurements are to be performed. Deviations in contact angle of more than
±10° from a line perpendicular to the surface will result in an underestimation of the frequency shift, meaning that the tissue will be regarded as stiffer than it really is. This result is important as the flat silicone models have a very even surface, which makes a controlled contact angle possible. Biological tissue can have a rough and uneven surface, which can lead to unintentional deviations in the contact angle. The magnitude of the stiffness parameter is favoured by a high indentation velocity compared to a low.

The evaluation of this measurement system has shown that it is possible to distinguish between soft and stiff silicone models, which have been used in this initial phase of the study. A new feature in this measurement system is the fixture that makes measurements on spherical objects possible and the possibility to vary the angle of contact. This is promising for future studies and measurements on whole prostate in vitro. A future application for this measurement system is to aid surgeons performing radical prostatectomy in the search for tumour tissue on the capsule of the prostate, as the presence of tumour tissue can indicate that the cancer has spread to the surrounding tissue.
1. Original papers

This licentiate thesis is based on the following papers, which are referred to by Roman numerals. The papers are reprinted with permission from the publisher when applicable


Peer-reviewed conference publications of relevance, but not included in the thesis.


2. Abbreviations

\( \Delta f \)  
frequency shift

\( F \)  
force

\( I_Z \)  
impression depth of interest

\( I_M \)  
length of sensor movement

\( n \)  
number of measurements

\( v_i \)  
indentation velocity

\( \alpha \)  
contact angle

\( \varepsilon \)  
error

\( \partial F / \partial \Delta f \)  
stiffness parameter

\( p \)  
Pearson’s correlation coefficient

\( \text{PLL} \)  
phase-locked loop

\( R^2 \)  
Degree of explanation of a model

\( \text{SD} \)  
standard deviation
3. Introduction

3.1 General background

The most common form of cancer among men is prostate cancer. In the US, the American Cancer Society estimates that about 241,700 new cases will be diagnosed in 2012 [1]. In Sweden, prostate cancer stood for 33.4% of the new cases of cancer in 2010 as about 9,700 men were diagnosed [2]. The diagnostic methods used to detect prostate cancer vary. Common methods are rectal palpation and a test for the prostate specific antigen (PSA), which can be followed by a multiple systematic biopsy. The outcomes of these tests are important for decisions regarding what treatment is thought to give the best result in each case. For the case when it is necessary to perform a radical prostatectomy, it is of interest to investigate the presence of cancerous tissue on the capsule of the prostate gland. Such presence might indicate that the cancer has metastased. This licentiate thesis describes a flexible measurement system with which this can be done in vitro at the time of surgery.

The stiffness of soft human tissue can vary due to different physiological conditions and diseases, and a change in the biomechanical properties occurs. Tumour tissue is usually harder than healthy tissue [3, 4]. The possibility to use piezoelectric resonance sensors in medical research in order to detect differences in stiffness in soft tissue has been shown in previous studies [5, 6].

3.2 Piezoelectric resonance sensors in medical applications

Piezoelectric resonance sensors have been used to measure the differences in stiffness and elasticity of the skin in order to detect oedema and lesions [7, 8] and to detect lymph nodes containing metastases [9]. Resonance sensors have also been used to measure the stiffness of the liver to indicate liver fibrosis [10]. Jalkanen et al. [3, 4] have made studies on prostate tissue in vitro that show the possibility to differentiate between benign and malignant tumours. In studies by Lindberg et al. [11], and Eklund et al. [12] a resonance sensor probe was attached to an instrument based on a counterbalance arrangement. They used both silicone models and prostate tissue in vitro on which measurements of the frequency shift, \( \Delta f \), with constant applied force,
were done. A theoretical model that relates the measured stiffness through $\Delta f$ and $F$, to the Young’s elastic stiffness modulus of the measured object has been shown by Jalkanen et al. [13]. For evaluating tissue stiffness, he introduced the stiffness parameter $|\partial F/\partial \Delta f|$. A similar expression was used by Hallberg et al. [14], and Eklund et al. [15] to relate the intraocular pressure to $\Delta f$ and $F$, utilizing resonance sensors to measure eye pressure.

### 3.3 Silicone models of soft human tissue

For evaluation of new sensor techniques regarding human soft tissue characterization, silicone models have been found to be very suitable for preliminary research [4, 11]. Silicone models are preferable for this type of study as they can be mixed into different stiffness, and it is possible to enclose small pieces of harder or softer objects for the simulation of stiffness variations due to disease. Silicone models are also more stable over time than biological materials.

Biological tissue can show changes in its properties due to environmental conditions, and can start to dehydrate and degrade during the time of measurement. Its normal properties also change as it is removed for in vitro measurements. Biological tissue is viscoelastic, a combination of viscosity and elasticity. The ratio of this combination varies for different types of tissue [16]. Viscosity is the resistance that a certain material has against changing when subjected to a force. Elasticity is the property of a material to temporarily change shape during the time when it is subjected to a force. Viscoelastic materials usually show other properties, one of which is hysteresis, which is the difference in behaviour during loading and unloading of a force. Phipps et al. have demonstrated that the mechanical characteristics of healthy and malignant prostate tissue can be described by viscoelastic models [17].

### 3.4 A flexible resonance sensor measurement system

To further explore the potential of the resonance sensor method to diagnose the presence of prostate cancer on the capsule in vitro, an appropriate instrument is needed. Due to the spherical shape of the prostate, such an instrument should have a fixture that can hold and rotate the prostate. For reliable measurements on the uneven and curved surface of the prostate, the direction of the movement of the sensor must be adjustable to be able to control the contact angle, $\alpha$, to the surface of the measured object [III].
Studies have been done by using flat and spherical silicone tissue models, where the measured parameters $\Delta f$, $F$, and $|\partial F/\partial \Delta f|$, were studied.

### 3.5 Aims

The overall aim was to develop a sensor system for possible detection of cancer in soft human tissue, specifically prostate cancer. The specific aims of the studies presented in this thesis were:

- To design a flexible resonance sensor system with the possibility to measure on flat and spherical objects.

- To determine the performance of the system and maximum errors.

- To evaluate how the system parameters are affected by variations in contact angle and indentation velocity, using silicone models.
4. Materials and methods

4.1 Resonance sensor system

When a force is applied to a piezoelectric element, an electric potential difference occurs. This effect can be reversed, meaning that a piezoelectric element changes shape if an electric field is applied. If a sinusoidal electric field is applied, the piezoelectric element will start to oscillate. The piezoelectric resonance sensor used in these studies is divided into two piezoelectric elements, Figure 1. One part was used as a driving element that produces the oscillation. The other part of the sensor was used as a pickup to detect the vibrations from the oscillation, and this part was connected to a PLL (phase-locked loop) circuit. The signal from the pickup was constantly transferred to a feedback circuit where the phase-shift circuit ensured that a zero phase condition between the pickup and the drive signals was established. Hence the whole sensor was kept oscillating at its resonance frequency [5].

![Figure 1. A schematic illustration of the function of the piezoelectric resonance sensor in a measurement situation.](image)

When the tip of the sensor comes into contact with an object there will be a change in the frequency, $\Delta f = f - f_0$, where $f_0$ is the free resonance frequency of the element, and $f$ is the resonance frequency of the
element when in contact with an object. The sign of \( \Delta f \) depends on the material that the sensor comes into contact with. A soft material that can be deformed by the sensor will result in a negative shift, while a hard object will give a shift with a positive sign [5].

4.2 The measurement system

The new flexible measurement system that was developed had three translation stages with stepper motors, which were controlled by a PC and a LabView® (National Instruments, Austin, Texas, USA) program. Two translation stages, X and Y, were for movement in the horizontal plane. A third translation stage for vertical movement, Z, was mounted on a rotational stage to enable different contact angles between the sensor and the measured object [III], see Figure 2.

![Figure 2. A schematic side view of the basic components of the measurement system. The movement of the translation stages are controlled from a PC.](image-url)
4.3 Technical setup

The two translation stages for the horizontal movements (M4424; Parker Hannifin Corporation, Daedal Division, Irwin, PA, USA) were modified with stepper motors (17HD1008; Moons’, Shanghai, P.R. China) with a resolution of 2.5 µm, attached to the micrometer screws. A smaller translation stage (VT-21: Micos, Irwin, PA, USA) for vertical movement, with a resolution of 2.5 µm, was controlled by a motorized stage controller (Pollux Box; Micos, Irwin, PA, USA). The manual rotational stage (NT55-030; Edmund Optics, York, UK) had a resolution of 0.5°, and made it possible to rotate the vertical translation stage ±90°.

The sensor used for measurements of $\Delta f$ consisted of a piezoelectric cylindrical element of lead zirconate titanate, PZT (Morgan Electro Ceramics, Bedford, Ohio, USA). The cylinder was 15 mm long with an outer diameter of 5 mm and inner diameter of 3 mm. The only part of the sensor that came into contact with the measured object was a hemisphere made of polyether-ether-ketone (PEEK) which was glued to one end of the cylinder. The piezoelectric element and a preloaded force sensor (PS-05KC; Kyowa, Tokyo, Japan) were mounted inside an aluminium casing, Figure 3. The force sensor and the piezoelectric element were calibrated before the study to get valid calibration constants for the voltage-to-force, and voltage-to-frequency conversions [III].

![Figure 3. A side view of the complete sensor head. The piezoelectric element is held in position in the sensor housing by soft springs. The force sensor is connected to the piezoelectric element by a thin rod.](image-url)
The signals from the force sensor and the piezoelectric sensor were collected and passed to a PC at a sampling rate of 1 kHz using a data acquisition card (NI6036E; National Instruments, Austin, Texas, USA).

The vertical translation stage could be mounted on the X-Y base in two different positions, enabling measurements on flat and on spherical objects. For measurements on flat objects, there was a platform with threaded holes and brackets for secure attachment, Figure 4. For larger objects, the height of the platform could be altered, or it could be removed completely. Spherical objects could be mounted in a fixture that could rotate around its horizontal axis. The clamping force could be measured by a cantilever strain gauge (CEA-06-240UZ-120, Measurements Group Inc. Raleigh, NC, USA).

**Figure 4.** The complete measurement system. The sensor head is in position for measurements on a spherical silicone model. 1) The vertical translation stage, which is mounted on a manual rotational stage. 2) The sensor head. 3) A silicone model in the fixture for spherical objects. 4) Translation stages for horizontal movements. 5) A flat silicone model attached to the measuring platform.
4.4 Tissue models made of silicone

The silicones used for the models simulating soft human tissue were made from a two-component silicone mixture (Wacker SilGel 612; Wacker-Chemie GmbH, Germany). This silicone has been described as suitable in earlier studies [4, 11, 18]. The two components can be mixed at different ratios by weight, in accordance with the manufacturer’s instructions, thereby obtaining silicones with different stiffness [19]. The two components were weighed on a laboratory scale (Sartorius BL 310, Sartorius GmbH, Göttingen, Germany) with a precision of 0.01 g [III].

The degrees of stiffness for the different mixing ratios are presented as cone penetration values according to DIN ISO 2137 using a 150g hollow cone [19], Table 1.

Table 1. The mixing ratios for the silicone, according to manufacturer’s instructions.

<table>
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<th>Mixing ratio A : B, by weight</th>
<th>Penetration value (mm x 10^3)</th>
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<tr>
<td>4 : 3,75</td>
<td>Softest</td>
</tr>
<tr>
<td>4 : 3,5</td>
<td></td>
</tr>
<tr>
<td>4 : 3,2</td>
<td></td>
</tr>
<tr>
<td>4 : 3,0</td>
<td></td>
</tr>
<tr>
<td>4 : 2,5</td>
<td>Hardest</td>
</tr>
</tbody>
</table>

Flat silicone discs with different stiffness were cast in Petri dishes (diameter 87 mm, height 13 mm). Small pieces of silicone of a stiffer mix could be enclosed to simulate tissues of different stiffness.

Spherical tissue models were cast using a table tennis ball with a diameter of 40 mm as a mould [II], Figure 5.

![Figure 5. Illustration of how a table tennis ball was used as a mould for casting spherical objects. To the right is a picture of a spherical silicone model with an enclosed piece of stiff white rubber.](image-url)
To simulate an enclosed minor region with harder material near, but not directly on the surface of the sphere a small piece of a material of different hardness was arranged on a thin (0.25 mm) wire inside the ball before pouring in the silicone. The wire could be removed after the silicone was cured and the plastic table tennis ball was carefully cut open to take out the silicone model.

4.5 Measurement setup

4.5.1 The measured data

For every measurement it was necessary to be able to determine when the sensor touched the surface of the object to decide the absolute values for the parameters $\Delta f$, $F$ and $I_Z$. This was achieved by moving the sensor in small steps towards the surface, and using a change in $\Delta f$ as an indicator of contact [III]. When contact was confirmed, the direction of the sensor movement was reversed to a pre-set distance from the surface. This distance could be set in the LabView® program. Larger distances were necessary for sticky silicones.

The logging of data started after the reverse movement, when the sensor started to move towards the surface again, and into the material at a pre-set $v_i$. The movement stopped when the pre-set length of movement $I_M$, had been reached. Both $v_i$ and $I_M$ were selected in the settings for the stepper motor in the LabView® program.

The time for a typical measurement was four seconds, during which the sensor was at a standstill for two seconds after the pre-set $I_M$ was reached. By choosing an $I_M$ that was larger than the planned interval of $I_Z$, it was possible to select data for different $I_Z$ from one measurement sequence. For the measurements, $I_Z$ was chosen to 0.20 mm and 0.38 mm.

For each measurement, the average of the first 100 samples of the voltage signal from the resonance sensor was used to calculate the free resonance frequency $f_0$, i.e. when the sensor was in mid-air and without contact with the surface [III]. The $\Delta f$ that occurred at contact and during the impression phase was calculated as the difference between the logged $f$ and $f_0$. The preloaded force sensor gave a bias in the voltage signal, which also was subtracted by using the average of the first 100 samples in order to calculate $F$.

To identify the collected data for $\Delta f$ and $F$ at a certain $I_Z$, the $v_i$ and the sampling rate were used to calculate the number of samples that lay between the moment of confirmed contact with the surface and the $I_Z$ of interest.
The parameter $|\partial F / \partial \Delta f|$ was calculated by linear regression of $F$ and $\Delta f$ with respect to $I_Z$ and $v_i$ for each measurement. The number of data samples used for the linear regression of $|\partial F / \partial \Delta f|$ depended on $v_i$, but was always at an interval of $I_Z \pm 0.05$ mm [III].

4.5.2 Measurements on flat silicone models

The measurements in Paper I were made perpendicular ($\alpha = 0^\circ$) to the surface of flat silicone models, Figure 6. Measurements were made with 10 repetitions on five flat silicone models with different stiffness, see Table 1. A period of two minutes between each impression was allowed for the silicone to regain its original shape. The $I_M$ was set to 1 mm and the $v_i$ used was 5 mm/s. To verify if the measurement system could distinguish between the different silicone samples, $\Delta f$ was collected at a constant $F = 40$ mN [I Fig 4].

Figure 6. A side view of the sensor set for measurements on a flat silicone disc in a Petri dish. 1) The manual rotational stage. 2) The vertical translation stage. 3) Sensor head. 4) Silicone disc in a Petri dish. 5) Platform with brackets holding the Petri dish.
In Paper III, one part of the study was focused on evaluating the measured parameters, $\Delta f$, $F$ and $|\partial F/\partial \Delta f|$, for variations in $\alpha$ between the sensor and the silicone surface. For this, two flat silicone models were used of different stiffness with cone penetration values of 163 mm x 10^{-1} and 49 mm x 10^{-1}, see Table 1.

It was important to ensure that it was only the hemispherical tip, and not the piezoelectric element, that came into contact with the surface of the measured object. For this reason, the maximum angle of contact, $\alpha_{\text{max}}$, had to be determined, Figure 7. For an $I_M$ of 1 mm, the $\alpha_{\text{max}}$ was calculated to be 36.8°, meaning that if $\alpha > \alpha_{\text{max}}$, the edge between the sensor tip and the piezoelectric element would penetrate into the silicone. For $I_M \leq 1$ mm, $\alpha_{\text{max}}$ would increase to angles outside the range of interest for this study. Larger $I_M$ were not used because it might damage the force sensor due to large $F$.

The interval of $\alpha$ studied was from 0° to 35°, and because of symmetry, only positive $\alpha$ was considered. Measurements were made six times for each $\alpha$, and the measured data for the $\Delta f$ and $F$ were taken at $I_M = 0.20$ mm and at 0.38 mm at $v_i = 5$ mm/s [III].

Figure 7. A schematic illustration of the sensor at different angles of contact with a surface. $I_M$ is the length of movement of the sensor (regardless of $\alpha$). $I_Z$ is the impression depth measured perpendicular to the surface of the measured object. The piezoelectric element has diameter, $d = 5$ mm, the spherical tip has radius, $r = 2.5$ mm. A line perpendicular to the plane corresponds to a contact angle $\alpha = 0^\circ$. 
4.5.3 Measurements on spherical surfaces

In Paper II, the measurements were made on a spherical silicone model. The position for the vertical translation stage was changed to a position reaching the fixture for spherical objects. A spherical silicone model made of soft silicone with cone penetration value 163 mm x 10^{-1} was held in position by two concave plates, Figure 8.

Two series of measurements were made. At first, the sensor tip was moved in a vertical direction towards the sphere, while in the second series the angle of the sensor movement was adjusted such that a perpendicular movement to the surface of the sphere was obtained. Measurements were made at nine points separated by 2 mm, in a straight axial line across the sphere. The points of contact on the silicone sphere were the same in both measurement series. The measurements with the vertical movement of the sensor towards the sphere resulted in varying $\alpha$. The different $\alpha$ towards the surface in the measured positions were calculated to be $0^\circ$, $5^\circ$, $11^\circ$, $17^\circ$ and $23^\circ$ to the left and right from the center position corresponding to $\alpha = 0^\circ$.

![Figure 8](image-url)  
**Figure 8.** The sensor in position for measurement at an angle towards a spherical silicone model clamped in the holder. 1) Sensor head, 2) Clamps holding the sphere, 3) Spherical silicone model, 4) Stiff rubber inclusion.
4.6 Maximum error estimates and statistical methods

The maximum error [20] was calculated for each measurement parameter, \( \Delta f \), \( F \) and \( |\partial F/\partial \Delta f| \) [III]. To calculate the absolute error in \( F \), \( e_F \), the voltage signal from the force sensor during calibration was measured using a multimeter and a laboratory scale. The effect of errors in the electronic circuits involved in the force measurement was included in the calibration. For estimation of the maximum error in \( f \), the voltage signal from the electronic circuit that kept the piezoelectric element at a constant resonance frequency was used. Data for this was collected at the time of calibration where a wave function generator and a multimeter were used. The maximum error for the parameter \( |\partial F/\partial \Delta f| \) was determined from the maximum errors of both \( \Delta f \) and \( F \) [III].

The maximum error in the movement of the sensor was also estimated. The error in \( I_M \) and \( I_Z \) consisted of two parts. From the collected data there was an uncertainty in finding a sample that corresponded to the instant at which the sensor came into touch with the surface of the silicone model, especially at low \( v_i \). The second part was due to the resolution of the stepper motor controlling the vertical translation stage [III].

The data in this study was subjected to a one-tailed t-test to test if the measured \( \Delta f \), \( F \) and \( |\partial F/\partial \Delta f| \) deviated by more than 10% from their respective values at \( \alpha = 0^\circ \). The calculated p-value of \( \leq 0.05 \) was considered significant for all statistical tests. The measured values in this thesis are presented as mean ± standard deviation (SD).
5. Results and discussion

5.1 Instrument performance and accuracy

A new flexible measurement system to detect areas of different stiffness in soft human tissue has been developed and presented. The new features for this system, compared to earlier systems [4, 11, 12, 18], are the possibilities to do measurements at different angles on flat or spherical objects, and that the velocity of the sensor movement can be varied. The performance of the measurement system has been evaluated.

Measurements were made in series of 10 on five flat silicone models of the same type of silicone, but with different stiffness [I]. The movement of the sensor was perpendicular to the surface of the silicone discs at a constant $F$ and at $v_i = 5$ mm/s. It was shown that the measured $\Delta f$ from the measurements on the different silicone mixtures was in compliance with measurements done according to the DIN ISO standard 2137 provided by the silicone manufacturer. The $\Delta f$ was linearly correlated ($R^2 = 0.99$, p < 0.05) to the cone penetration values used in the standard, Figure 9.

![Figure 9](image)

Figure 9. Measurements of $\Delta f$ (mean ± SD, n = 10) at $F = 40$ mN and at $v_i = 5$ mm/s on five flat silicone models with different stiffness with given cone penetration values.

The method for estimating the maximum error for each of the measured parameters is described in detail in Paper III. The maximum relative error
for $F$ was found on measurements on the stiff silicone, and was 1.05% of measured value. The largest error in $\Delta f$, 0.03% of measured value, was reached on soft silicone. The maximum error for $|\partial F/\partial \Delta f|$ was 1.08%, calculated from the maximum errors of both $\Delta f$ and $F$.

The largest errors for the measurement system were in $I_M$ and $I_Z$ as they were affected by the uncertainty in the estimation of the moment when the sensor came into contact with the surface. The smallest error was for measurements with low $v_i = 1$ mm/s and at the deepest indentation that was studied, $I_Z = 0.38$ mm. The largest error occurred for measurements at high $v_i = 5$ mm/s and a shallow indentation, $I_Z = 0.20$ mm. This gave an interval for the maximum error from 0.79% up to 12.50% of the intended impression depth. The accuracy of the stepper motor in the vertical translation stage gave a comparatively smaller error in $I_M$ and $I_Z$ of 0.38% to 0.72%, depending on the length of the sensor movement, which was not velocity-dependent [III].

### 5.2 Angular dependency

The measurements in Paper II on a spherical silicone model, showed lower values for $\Delta f$ when the sensor approached the surface at an angle deviating from the perpendicular, a decrease that increased with larger angles, Figure 10.

![Figure 10](image)

**Figure 10.** Measurements on a spherical tissue model made of silicone. One series of measurements where the sensor tip moved vertically towards the sphere, and one where the sensor tip moved perpendicular to each point of contact on the sphere. The figure shows $\Delta f$ (mean +/- SD, n=6) at different positions of the sphere at an impression depth of 0.2 mm.
Further studies of the angular dependency were made in Paper III. Measurements were made on two flat silicone models of different stiffness with an increased number angles deviating up to 35° from a line perpendicular to the surface of the silicone model. This showed that the absolute relative deviation in $\Delta f$, due to $\alpha$, was on average $\leq 10\%$ for $\alpha \leq 10^\circ$ (one-tailed t-test, $p < 0.05$), with a few exceptions, Figure 11.

![Figure 11](image)

**Figure 11.** The angular dependency of $\Delta f$. Measurements were made on the soft and the stiff flat silicone discs. The relative deviation in $\Delta f$ (mean ± SD, n = 6) from $\Delta f$ at $\alpha = 0^\circ$, i.e. $(\Delta f(\alpha) - \Delta f(\alpha = 0^\circ)) / \Delta f(\alpha = 0^\circ)$ for measurements at $I_M = 0.20$ mm and at 0.38 mm and for different $\alpha$. The horizontal dotted line at 0-level is a guide for the eye.

The results in Paper III regarding the angular dependency were found to be similar to a previous study made by Murayama [21]. He used a thin micro tactile sensor with a diameter of 10 $\mu$m. His conclusion is that the precision of the measured $\Delta f$ decreased as the contact angle increased. The reason for this is the change in contact area between the sensor and the measured object.

The measurements shown in Figure 11 are based on the pre-set $I_M$, for all $\alpha$. The results show that the impression perpendicular to the surface, $I_Z$, decreased with increasing $\alpha$. For this reason, data from a representative measurement series were recalculated to new $I_M$ so that $\Delta f$ could be selected at a constant $I_Z$ for all $\alpha$, Figure 12.
In previous studies [15, 22] it is shown that \( \Delta f \) is proportional to the area in contact with the measured object. Eklund et al. [15] used a sensor similar to the sensor described in this thesis, but with a larger contact area. His sensors had a contact area that varied from 5.3 to 13.7 mm\(^2\), whereas the interval in our study was 3.1 to 6.0 mm\(^2\). By the use of the relationship from his study, our measured data of \( \Delta f \) at constant \( I_M \) could be recalculated to correspond to \( \Delta f \) at constant \( I_Z \). Although these new values were closer to the values at constant \( I_Z \), the recalculation did not explain the whole deviation [III], Figure 12.

![Figure 12](image-url)

**Figure 12.** Comparison of \( \Delta f \) for \( I_M \) and \( I_Z = 0.38 \) mm on the softer silicone and recalculated \( \Delta f \) from constant \( I_M = 0.38 \) mm taking into account the decreasing contact area with increasing \( \alpha \).
The data for the angular dependency of $F$ (Figure 13) from the measurements presented in Paper III, showed a weaker dependency on $\alpha$, than for $\Delta f$, Figure 12. The data for $F$ at $\alpha$ from 1° to 35° were compared with the value of $F(\alpha = 0°)$. For the stiff silicone, $F$ showed stable values up to about $\alpha = 15°$ with a variation of $\leq 10\%$ in relation to $F(\alpha = 0°)$. The data analysis of the measurements of soft silicone showed a variation of more than $10\%$ already at $\alpha = 2°$ for the small $I_Z$. A high relative variation in $F$ on soft silicone may be the result of small absolute values of $F$, especially for low $I_Z$.

![Figure 13](image)

**Figure 13.** Measurements made on the soft and the stiff flat silicone discs at $I_M = 0.20$ mm and 0.38 mm and for different $\alpha$. A dotted line is placed at 0-level as a guide for the eye. The relative deviation of $F$ (mean ±SD, n=6) from $F$ at $\alpha = 0°$, i.e. $(F(\alpha) - F(\alpha = 0°)) / F(\alpha = 0°)$.

However, again the data were based on a constant $I_M$, which meant that the impression depth, $I_Z$, perpendicular to the surface decreased when $\alpha$ increased. In the same way as for $\Delta f$, new data from a representative measurement series were recalculated to new $I_M$ so that $F$ could be selected at a constant $I_Z$ for all $\alpha$, Figure 14. The vertical components of $F$ when $I_Z$ was held constant for all $\alpha$ were calculated and were expected to be near the value of $F(\alpha = 0°)$. The analysis showed that for $F$ at $\alpha > 10°$ there was a deviation from $F(\alpha = 0°)$, with increasing $\alpha$. This may be explained by mechanical friction forces between components inside the sensor head [III].
Figure 14. Data for $F$ at $I_M = 0.20$ mm and data for $F$ at $I_Z = 0.20$ mm on stiff silicone. The recalculated data for the vertical component of $F$ when $I_Z$ was kept constant at 0.20 mm are also shown.

The stiffness parameter, $|\partial F/\partial \Delta f|$, showed an angular dependency (Figure 15) similar to the one for $\Delta f$ shown in Figure 11. The relative deviation of $|\partial F/\partial \Delta f|$ with $\alpha$, compared to $|\partial F/\partial \Delta f|$ at $\alpha = 0^\circ$, was on average $\leq 10\%$ for $\alpha = 1 - 10^\circ$ (one-tailed t-test, $p < 0.05$).

Figure 15. Measurements made on the soft and the stiff flat silicone discs at $I_M = 0.20$ mm and 0.38 mm and for different $\alpha$. A dotted line is placed at 0 as a guide for the eye. The relative deviation in $|\partial F/\partial \Delta f|$ to $|\partial F/\partial \Delta f|$ at $\alpha = 0^\circ$ (mean $\pm$ SD, $n = 6$).
For diagnostic purposes, the parameter $|\partial F/\partial \Delta f|$ has been shown to be important for distinguishing differences in tissue stiffness [13], and larger differences in $\Delta f$ have a preferable effect on the magnitude of $|\partial F/\partial \Delta f|$, as it would increase the resolution. These results indicate stability against small, unintentional deviations (at least up to 10°) from a perfect perpendicular indentation.

Note that the studies reported in Papers I and III were made on flat silicone discs with an even and horizontally placed surface. Biological tissue will probably have a rough and uneven surface, which might lead to $\alpha$ deviating slightly from the intended perpendicular approach in each point.

### 5.3 Velocity dependency

In our studies reported in Papers I and II, a constant $v_i = 5$ mm/s was used. In Paper III we evaluated the effect of different $v_i$, on $\Delta f$, $F$ and $|\partial F/\partial \Delta f|$. Measurements were made on two flat silicone models with different stiffness. The $v_i$ used were 1, 2, 3, 4 and 5 mm/s, all for measurements perpendicular to the surface of the silicone, which meant that $I_M = I_Z$ and that the contact area between the sensor tip and the surface was constant.

The $\Delta f$ decreased with increasing $v_i$ [III Fig. 10a]. The relative difference in $\Delta f$ between silicones of different stiffness showed a decrease with increasing $v_i$, which was more apparent for $I_M = 0.38$ mm.

The measurements indicated that the values for $F$ were less dependent on $v_i$ [III Fig. 11a], compared to what was found for $\Delta f$. However, a significant difference in $F$ between the different silicones at each $I_M$, could be verified. The constant area in contact with the surface, as the measurements were made with a perpendicular approach to the surface, could be the reason for the low dependency of $F$ on $v_i$. 
The dependency of $|\partial F/\partial \Delta f|$ on $v_i$ showed an increase in $|\partial F/\partial \Delta f|$ when $v_i$ was increased from $v_i = 1 \text{ mm/s}$ to $v_i = 5 \text{ mm/s}$, Figure 16. The dependency was stronger for the soft than for the stiff silicone.

Figure 16. Measurements on silicone discs with two different stiffness and flat silicone discs at $I_M = 0.20 \text{ mm}$ and $0.38 \text{ mm}$. The $|\partial F/\partial \Delta f|$ (mean $\pm$ SD, $n = 10$) for different $v_i$.
6. Conclusions

6.4 Conclusions

A new flexible measurement system has been developed and its functionalities were evaluated on soft tissue silicone models. It was concluded that the measurement system could distinguish between silicones of different stiffness with repeatability. The measurements were made on flat and spherical silicone models.

The maximum errors for the system parameters were estimated, as well errors in the positioning of the sensor head relative to the measured object.

Further we conclude that the errors in the measured system parameters for contact angles up to about 10° was small, although the errors tend to increase for larger angles.

We also conclude that the indentation velocity affects the resolution of the measured parameters of silicones of different stiffness. A lower indentation velocity resulted in a higher resolution in frequency shift, but for the stiffness parameter the opposite was found.

6.2 Future

A common aspect in the studies presented in this licentiate thesis was to evaluate and ensure the function of the measurement system before further measurements on biological tissue take place. With these studies, we have come closer to our goal, which is to make measurements on human prostate in vitro, to detect cancerous areas on the capsule. Since prostate tissue samples, especially excised prostate glands, will probably have uneven and rough surfaces, the intended angle of the sensor to the tissue surface might vary unintentionally, the information regarding the contact angle is especially important.

A future application is to use the measurement system to aid surgeons at the time of radical prostatectomy. With a possibility to scan the capsule of the prostate directly after the prostatectomy, the future treatment of the patient could be decided sooner. The current situation is often to wait for microscope-based morphometric investigations. This new measurement system provides a method for assessment of the condition of the prostate.
7. Acknowledgements

I would like to express my sincere gratitude to the persons who have supported me in this work.

First of all, I would like to thank my supervisor Dr. Britt Andersson for introducing me to the world of a PhD student. Her encouragement and willingness to discuss problems that I have come across on the way have been invaluable. Her positive attitude and ability to see things from a different angle have been of great importance, as has also her help by being a co-author on my papers.

I also want to thank Professor Olof Lindahl and Dr. Ville Jalkanen in their role of co-supervisors. They have always been helpful and willing to help me with obstacles that I have stumbled on. They have also been very important co-authors on my papers.

Furthermore, I would like to express my gratitude to Sven Elmå, who helped with the manufacturing of many mechanical components as well as Johan Pålsson, who helped with the software LabView®, and Lars Karlsson who helped with the electronics.

I would also like to thank staff at Bioresonator AB for help and support.

The study was supported by The Industrial Doctoral School at Umeå University, BioResonator AB, and by grants from Objective 2 North Sweden-EU Structural Fund.

And last but not least, I would like to thank family and friends who have supported me through this time.
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Summary of papers

Paper I

The paper describes a flexible measurement system using piezoelectric resonance sensor technology developed for measurements on both flat and spherical objects. The study presents the newly developed measurement system and describes how it was possible to distinguish between five flat silicone discs with different stiffness through measurements of the frequency shift and the applied force. The movement of the sensor was perpendicular to the surface of the silicone disc and the indentation velocity of the sensor was 5 mm/s.

It was shown that the measured frequency shift from the measurements on the different silicone mixtures was in compliance with measurements done according to the DIN ISO standard 2137 provided by the silicone manufacturer. The frequency shift was found to be linearly correlated with the cone penetration depth used in the standard ($R^2 = 0.99$, $p < 0.05$). The conclusion of the evaluation was that the measurement system could distinguish between silicones of different stiffness with repeatability. A further evaluation of the function when measuring spherical objects is presented in Paper II.

Paper II

The measurement system was built so that it could be used for measurements on spherical objects, not only on flat objects as was described in Paper I. In this paper, the measurements were made on a spherical tissue model with a diameter of 40 mm made of a semi-soft silicone. At first, measurements were made with the sensor movement vertical towards each measuring point, which were positioned along a straight line across the sphere, along the axis of rotation. Secondly, measurements were made perpendicular to the surface at the same measuring points as in the first measurement series. This could be done by the use of the rotational stage. The indentation velocity was 5 mm/s. The set-up of the measurements resulted in a different contact angle between the sensor tip and the surface of the silicone in each measurement point due to the shape of the spherical surface. This was compared to when the sensor movement was kept vertical.
The angle of contact was perpendicular to the surface at midpoint, but showed an increasing deviation as the position of the selected measurement points came further away from the midpoint.

The results showed that the frequency shift from the vertical measurements deviated systematically from the measurements made perpendicular to the surface of the silicone. The measurements with a contact angle that deviated from the perpendicular underestimated the frequency shift. For the applied force, the two measurement series showed a similar appearance, meaning that the force sensor seemed to be less sensitive for the deviating contact angles that were used in this study. The conclusion was that the measurement system could be used for measurements on spherical objects, and that it was important to keep the sensor movement perpendicular to the surface of the measured object. The angular dependency of the frequency shift and applied force is reported in Paper III.

**Paper III**

Further measurements were made on flat silicone models to evaluate the dependence of the frequency shift, applied force and the stiffness parameter on the contact angle, the indentation velocity for different impression depths, $I_z$. The overall error of the resonance sensor measurement system was also to be determined. Measurements were done on two silicone models of different stiffness, with the indentation velocities ranging from 1 mm/s to 5 mm/s, and contact angles varying up to 35° from a line perpendicular towards the surface.

The results showed velocity dependence for the stiffness parameter, a higher contrast between the silicones with different stiffness at higher indentation velocity was noticed. This was preferable as the stiffness parameter has been found to be an important parameter for diagnostic purposes. The maximum errors for the measured parameters were generally small compared to the magnitude of the measured values, except for the relative error in the impression depth, which was 12.5% when the high indentation velocity was used. The results also showed that the three measured parameters: frequency shift, applied force and the stiffness parameter were all dependent on the contact angle. The conclusion was that deviations in the contact angle from the perpendicular can be accepted up to ± 10°, a larger deviation in contact angle resulted in unwanted errors leading to an underestimation of the frequency shift. This could lead to a misinterpretation of the condition of the measured tissue, i.e. that the tissue seems stiffer than it really is.