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Optical fiber probe for prostate cancer screening: *ex vivo* study

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ABSTRACT

We developed a miniaturized optical probe, based on a customized Fiber Bragg Grating, for mechanical characterization of biological tissues with sub-millimeter spatial resolution. The probe is integrated inside a metallic cannula (16 gauge) used for clinical applications, and it is driven by a robotic arm (KUKA LBR Med 7). The optical sensor has a resolution of less than 1 mN and measures the force on controlled tissue indentations. The functionality of the sensor was assessed by means of different tests carried out on real prostates obtained from radically surgeries of patients at different stages of the carcinoma (Gleason score from 6 to 8). Specifically, in this work, we demonstrate that our system provides results that are on line with to the biopsy analysis performed before and the surgery. Our findings lay the foundation for the development of compact optical fiber probes, with size compatible with needle/catheter, able to perform *in vivo* mechanical characterizations of the prostatic tissue with high sensitivity and spatial resolution.

Keywords: Fiber Bragg Gratings, robotic arm, sensing, mechanical characterization, prostate, cancer

1. INTRODUCTION

Tissue elasticity is a biomarker for diagnosing and predicting prostate cancer [1]. Because malignancy alters the morphology and mechanical properties of the prostate, the digital rectal examination is utilized as the initial diagnostic test. The physician currently performs this examination manually, with an unsatisfactory positive predictive value. It is anticipated that a more objective and spatially selective method will improve disease prediction and comprehension.

Currently, research efforts have focused on two major groups of assessment: imaging techniques (i.e. sonoelastography, ultrasounds or magnetic resonance elastography) and mechanical methods (using quantitative elasticity values to ascertain stiffness or elasticity, which can change in response to disease states) [2]. There is also considerable potential in combining both imaging and mechanical measurement. Concerning mechanical methods, in the last decades several solutions have been proposed. They essentially rely on the use of conventional force sensor technologies (load cells, piezo-resistive and resonance sensors) but the dimension of the overall system may prevent their use in *in vivo* applications.

In this scenario, optical fiber sensors are particularly appealing due to their inherent properties such as compact size, biocompatibility, non-toxicity, chemical and electromagnetic inertness. Concerning tissue mechanical characterization applications, optical fiber sensors based on both Fabry-Perot interferometers [3] and fiber Bragg Gratings (FBGs) [4,5] have been proposed.

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Specifically, an optical dynamic instrumented palpation sensor has been recently reported for the specific case of prostate cancer screening [3]. The optical fiber probe is made of a dynamically actuated membrane sensor based on a Fabry–Pérot interferometer. In all the above mentioned systems, optical fiber sensors are integrated in complex mechanical packaging that enhance the sensitivity at the expenses of the overall size (in the order of several millimeters).

In this framework, here we propose a miniaturized indenter based on a customized Fiber Bragg Grating suitably integrated inside a 16-gauge metallic cannula, and moved by a robotic arm. The developed sensor is an evolution of another device developed for the epidural space identification [6, 7].

The functionality of the developed sensor was previously assessed by means of different tests carried out on silicone membranes, phantom tissues mimicking different stages of the prostatic carcinoma, and also preliminary *ex vivo* experiments on real organs (healthy and unhealthy prostates) obtained from radical surgeries [8]. Here we carried out a further *ex vivo* study on three real prostates with different stages of the carcinoma (Gleason score from 6 to 8). We demonstrate that our system is able to provide results that are on line with to the biopsy analysis performed before and the surgery elasticity coefficients. Our device may open new horizons for early diagnosis and enhanced diagnostic accuracy of prostate cancer.

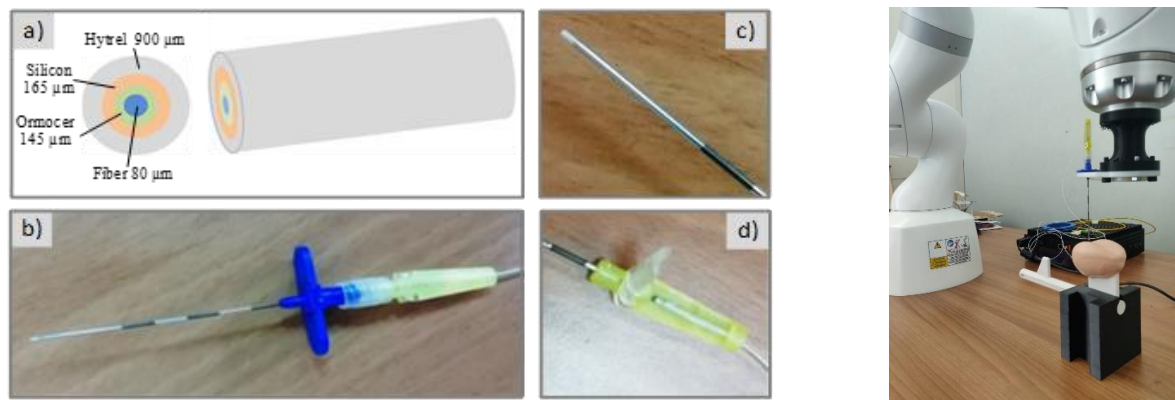


Figure 1. The developed optical fiber system (details in the text).

2. METHODS

2.1 The force sensor (calibration and interrogation unit)

The optical probe is made of an FBG (provided by FBGS Technologies GmbH) written in an 80 μm fiber by means of the draw-tower process: the FBG is coated by a Hytrel layer with an overall diameter of 0.9 mm. Thin layers of Ormocer and Silicone are used as buffer layers to improve the adhesion between silica glass and Hytrel (fig 1a). The FBG is integrated in a metallic cannula (fig 1b) with the optical fiber tip that comes out of 2 mm (fig 1c) in order to use the probe as indenter. The optical cable is locked to the cannula with a clamp-style connector (fig 1d), that firmly holds in position the probe so that it can be compressed while protected by the cannula. A standard luer lock adapter guarantees the connection of the clamp-style connector to the metallic cannula. The optical probe is connected to a commercial interrogation unit (Hyperion Optical Sensing Instrument si155) in order to measure and register the Bragg wavelength shift as a function of time during indentation experiments. A calibration procedure has been developed to find the correlation factor between the optical probe wavelength shift and the force applied on its tip. The probe sensitivity ($\Delta\lambda/\Delta N$) was found to be 1031 pm/N, details are provided in ref [8]. The sensor resolution is thus estimated to be 0.97 mN that is the ratio between the sensitivity (1031 pm/N) and the interrogator resolution (1 pm).

2.2 Experimental methodology: indentations driven by the robotic arm

The indentation tests were performed by moving the optical probe with a robotic arm (KUKA LBR Med 7) with the aim to accurately control the indentation depth (fig. 1e). To this aim, a customized holder for installing the optical probe on the robot end effector was realized by means of a 3D printing system. During indentation tests the prostate models have been suitably blocked in position by using a 3D printed holder. The phantom tissues were indented over more than 50 points separated by ~ 5 mm one from each other. The time interval between two consecutive indentations was set to 50 seconds. The indentation depths were determined starting from a zero-value that was determined through a force control algorithm, also referred to as admittance control, that allows to automatically detect a contact between the probe and the

prostate under analysis. Starting from a points' map, generated on a virtual x-y plane collocated some centimeters under the prostate, through admittance control the robot end effector and, then, the probe get closer to the prostate until a contact is detected. Once in contact, the robot stops itself and sets the reached position as the starting point for the indentation analysis. Details on the admittance control strategy are described in ref [8]. The indentation depth was set to 4 mm for all the points while the indentation speed was 0.2mm/s. Following the standard of the 12-core transrectal ultrasound-guided prostate needle biopsy, each prostate was indented on 12 different points pertaining to 12 different areas (4 on the Base, 4 in the Midland and 2 on the Apex zone, as shown in Fig. 7d). Approximately 18 indentation points were chosen in each of the three zones.

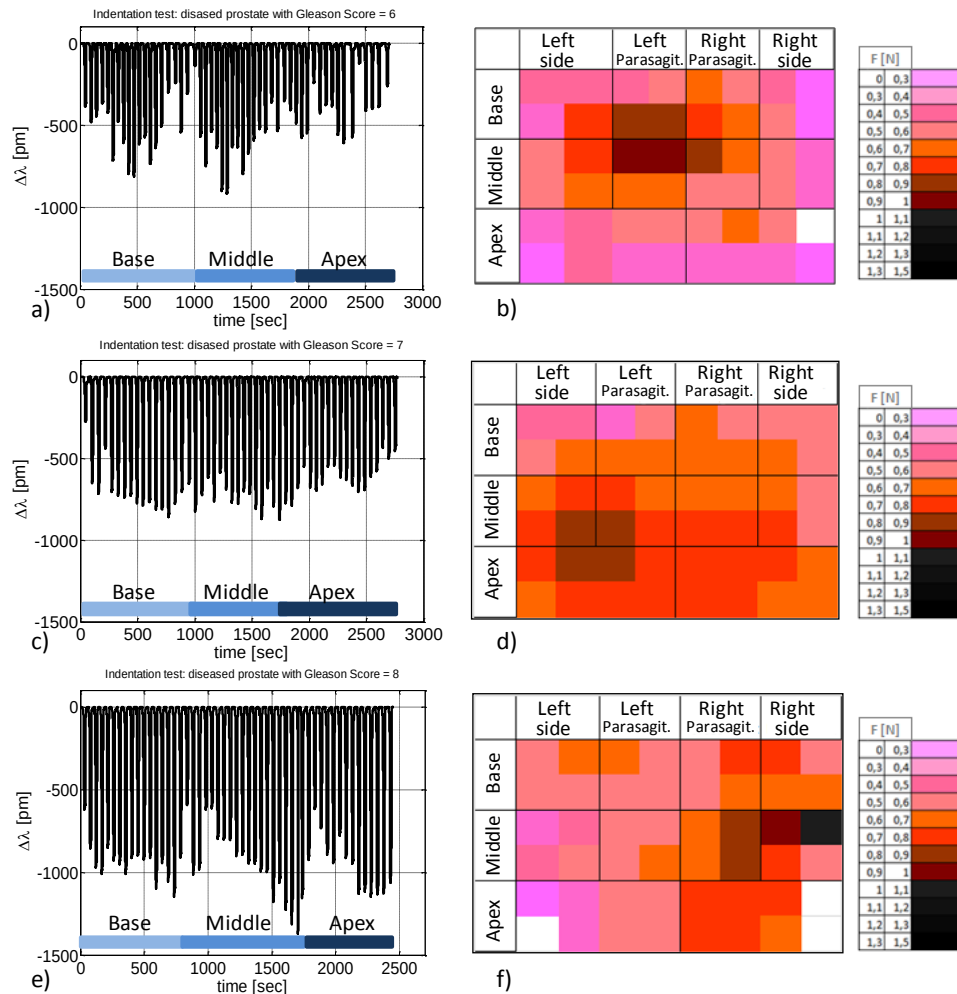


Figure 2. Sensorgrams (Left side) and color maps of the corresponding measured force values (right side) during the indentation tests of deseeded prostates with Gleason Score 6 (a-b), 7 (c-d), 8 (e-f)

3. RESULTS AND DISCUSSION

As previously mentioned, the developed probe was validated by carrying out indentation experiments on real prostates obtained from radical surgeries of patients. In particular, three real prostates were here analyzed with a different carcinoma stage. The sensorgrams (i.e. the wavelength shifts as a function of time) registered during the three *ex vivo* tests, are shown in Fig. 2a, Fig 2c and Fig. 2e for diseased prostates with Gleason score 6, 7 and 8, respectively. The Bragg wavelength shifts were evaluated as the difference between the point where the 'contact' force is measured and the minimum value. Starting from the wavelength shift the force values are derived by taking into account the probe sensitivity coefficient measured during the calibration process. The results are shown in figure 2 as color map (fig. 2b b and f). Darker Pixels correspond to high force (averaged) values measured in correspondence of harder and thus

malignant areas. Interestingly, the color maps derived from optical measurements are similar to those evaluated by the pathologist during the post-surgery biopsy carried out on the same glands immediately after the optical characterization (indentation) was completed. Figure three shows the force values measured in all the indentation point of the three prostates. Dotted lines represent the average values over the whole organ (533, 719 and 1015 mN), that are consistent with the prostate Gleason score (6, 7 and 8 respectively).

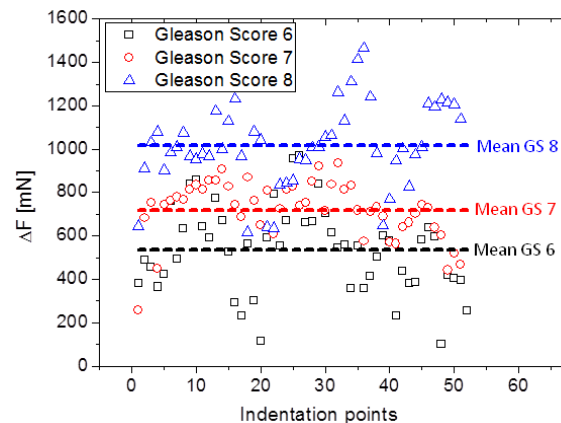


Figure 3. Comparison of the force values measured during the indentation tests of prostates with different Gleason Scores (variable from 6 to 8)

4. CONCLUSIONS

In this work, we have presented an optical fiber probe for mechanical characterization of prostatic tissue. The optical probe is made of a customized FBG used to measure the force acting on its tip during the indentation of specific tissue points with a sensitivity of about 1 nm/Newton. The probe is suitably integrated on a robotic arm that allows to achieve a fully controlled movement. *Ex vivo* tests on real prostates obtained from patients were carried out. Our results demonstrate that our system is able to discriminate between unhealthy prostatic glands with different Gleason score. These results lay the foundation for the development of an optical fiber probe to be directly integrated into biopsy needles to perform *in vivo* measurements of prostatic tissues elasticity. The small dimensions (probe diameter of 0,9mm) may allow achieving unprecedented levels of spatial resolution making possible to identify sub millimeter sized prostatic carcinoma arising at the early stages.

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