Fabry-Pérot based refractive index optical fiber sensor for measurement of oxygen concentration levels in hypoxic tumors during radiotherapy treatment

Charusluk Viphavakit*[a], DineshBabu Duraibabu[a], Sinead O'Keeffe[a], Elfed Lewis[a]
[a]Optical Fibre Sensors Research Centre, University of Limerick, Limerick, Ireland

ABSTRACT

An optical fiber sensor based on Fabry-Pérot interferometer to measure the refractive index changes due to oxygenation level changes in hypoxic tumors for radiotherapy treatments is proposed. The sensors have an outer diameter of 220µm with a 20-30µm length air-cavity and a 30µm thickness end cap located at the tip of the sensor. The sensors are used to measure the phase change in the received optical spectrum when there is a change in refractive index using a Fast Fourier Transform based analysis method. The refractive index change is measured in order to determine the oxygenation level in hypoxic tumors. In this paper, different concentrations of iso-propanol solution are prepared to produce refractive index values between 1.3438 and 1.3655 in order to mimic the refractive index of hemoglobin. The sensors are coated with a 100 nm thick gold layer and a comparison is made with non-coated sensors. The coated sensors have a resolution in order of 10^{-3} RIU.

Keywords: Fabry-Pérot interferometer, refractive index sensors, hypoxic tumors.

1. INTRODUCTION

Hypoxic tumors are solid tumors which are characterized by a lower oxygen level (0.3-2.4% of O_2) compared to the surrounding tissue (3.9-6.8% of O_2) [1-3]. They are commonly found as a form of cancer in lung, liver, stomach, colorectal, breast and prostate. The amount of oxygen in hypoxic tumors is related to the partial pressure of oxygen (pO_2) which can be used to distinguish the hypoxic tumors from non-hypoxic tumors and healthy tissue. The hypoxic tissue has a typical pO_2 value of 24-1.8mmHg while healthy tissue has a pO_2 value in the range 30-51.6 mmHg [1-3]. There exists a commercial sensor (OxyLite) [4] which has been developed to measure the pO_2 in tissue using a fluorescence quenching technique, but this cannot be used inside the human body due to FDA approval issues. Additionally, errors occur at high O_2 concentrations due to the non-linear relationship that exists in the sensor response at the higher O_2 concentration. Treatment of the hypoxic tumors can be undertaken by radiation therapy such as Intensity Modulated Radiation Therapy (IMRT) which applies the radiation dose directly to the tumors. In this case radiation dose has to be critically optimized in order to destroy the tumor cells but prevent damage to nearby healthy tissue especially organs. Hypoxic tumors are known to respond differently i.e. less favorably to radiation therapy than the non-hypoxic cases and this poses a significant problem when implementing radiotherapy oncology treatment in patients.

Currently, there are no sensors available that are capable of measurement in close proximity to the tumor *(in-vivo)* and in real-time during radiation treatment i.e. as the radiation dose is delivered. This work is focused on developing a sensor to assist accurate diagnosis and real-time monitoring of radiation dose in the treatment of hypoxic tumors in prostate cancer. A Fabry-Pérot based optical fiber based sensor is presented in this paper which is capable of measurement of refractive index changes within tissue. Optical properties of light such as absorption and scattering in blood depend on the refractive index of erythrocytes (red blood cells) which is defined by the concentration of hemoglobin in the red blood cells [5]. Hemoglobin is a globular protein which transports the oxygen in blood and its refractive index is known to vary with oxygenation level [6]. Therefore, the oxygen level in the hypoxic tumors and surrounding healthy tissues can be indirectly measured from the refractive index of hemoglobin. According to the small size and compact structure of optical fiber sensors based on the Fabry-Pérot interferometer, they can be integrated with biopsy needles which is a medical tool routinely used in cancer diagnosis and therapy. Also in the case of Brachytherapy the sensors can be inserted within the standard Brachytherapy seed delivery needles. In addition, the optical fiber sensors are made of passive material which is glass and coated with gold which is biocompatible. Therefore, the sensor can be used as an

*charusluk.v@gmail.com; phone 353 85-190-5846; www.ofsrc.ul.ie

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invasive tool to access within the tumors while receiving the radiation treatment allowing real-time monitoring and optimization of the radiation dose in the radiotherapy.

For the initial measurement, the sensors have been used to detect the change in refractive index for a range of concentrations of aqueous iso-propanol solutions. The iso-propanol solutions were prepared to have a refractive index range between 1.3438 and 1.3655 to correspond closely with the refractive index of hemoglobin which can vary from 1.3463 to 1.3471 in the near infrared region (NIR) [6]. Gold was used as the material to coat the tip of the sensor in order to enhance the interaction with hemoglobin which transports the oxygen level in the red blood cells [7-9]. This paper also includes a comparison of the gold-coated sensors and non-coated sensors with different refractive index of iso-propanol solutions. In the case of the Fabry-Pérot structure, the output signals are observed as an interference pattern and hence contain information regarding phase as well as amplitude. In order to monitor the phase variation from the interference pattern when there is the change in refractive index, a Fast Fourier Transform (FFT) algorithm was used. The FFT method is independent of signal amplitude allowing a simple phase based measurement as the amplitude (intensity) control and wavelength evolution tracking are not required.

2. DESIGN AND FABRICATION

The Fabry-Pérot based optical fiber sensor is an all-silica glass design comprising single mode fiber (SMF-28E), multimode fiber (MMF) and a 220µm diameter capillary. The schematic construction of the sensor is shown in Figure 1a). The sensor is similar in construction to the pressure sensor described by Poeggel et al [10] except the flexible thin glass diaphragm has been replaced by a relatively thick (15 and 27 µm were used) glass inflexible end cap. The end cap formed from the MMF as described in Poeggel et al [10] is of such a thickness that polishing can be undertaken by purely mechanical means i.e. there is no need for wet etching.to achieve the desired thickness. A 100nm thick gold layer was coated at the tip of some of the sensors using a sputtering technique for which it was necessary to include a 5nm thick titanium layer on the glass as an adhesion layer.

The output signal of the Fabry-Pérot based sensors is an interference pattern which is a function of cavity width, refractive index of the cavity and reflectivity of reflecting surfaces as presented in equation (1) [11].

$$T = \frac{(1-R)^2}{1-2R\cos(4\pi nd/\lambda)+R^2} \qquad (1)$$

where T is transmittance, R is reflectivity of the reflecting surfaces calculated by Fresnel equation [12], n is the refractive index between two reflecting surfaces, d is the cavity width and λ is the operating wavelength. In this case, the cavity is air filled ($n_{air} = 1$) and the cavity width is in the range 20 -30 µm (Figure 1a)). The end cap (diaphragm) thickness was selected to be at least 15 µm so that the sensors were not affected by intra tissue pressure. Therefore, the Fresnel reflection is only a function of refractive index of the sensing region ($n_{sensing}$), as this is the only component that influences the change of the interference pattern. An optical microscope image of the fabricated Fabry-Pérot based sensor is presented in Figure 1b.

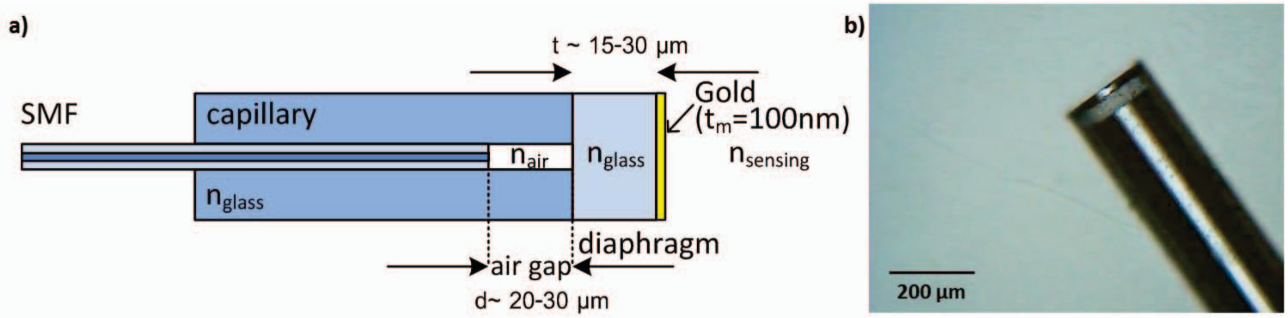

Figure 1: a) Schematic of Fabry-Pérot based optical fiber sensor to measure the change in refractive index. b) Optical microscope image of the fabricated Fabry-Perot based sensor.

3. EXPERIMENTAL RESULTS

The Fabry-Pérot cavity based optical sensors were designed to be able to measure small phase variations in the received optical signal when there is a change of the refractive index in the sensing region external to the tip of the sensor. It is therefore intended that the sensors are ultimately capable of measuring oxygen level in hypoxic tumors and surrounding tissue for diagnosis and monitoring oxygen level during the radiation treatment. In this paper, the sensors were initially tested with water (n_{water}=1.336) and three different concentrations of isopropanol solution. The solutions have refractive index of 1.344, 1.352 and 1.365 which are measured by the refractometer. This range of refractive index is sufficient to mimic the range of refractive index of blood and tissue which is known to vary from 1.3463 to 1.3471 [6].

The output signal of the sensor is a reflected spectrum corresponding to the interference pattern across the full range of interrogating wavelengths [10]. With the change of refractive index arising from the different solutions, the interference pattern (reflected spectrum) is changed causing phase variations to occur. In this work, an in-house developed FFT algorithm was used to monitor the phase variations. The FFT shows the frequency content of the fringe pattern within the spectral data including terms of frequency and phase. In this case, water is considered as a reference solution so the peaks of FFT for water are located to obtain the reference phase angle. With different solutions, the phase variations of the output signal can be obtained by retrieving the phase from the FFT at the reference peak location. The FFT of three different iso-propanol solutions with the reference location is presented in Figure 2a). It shows the changes in frequency distribution when the sensing medium alters its refractive index from which the phase shifts are derived. The resulting phase shift versus refractive index value is shown in Figure 2b) for two end cap thickness values of 15 and 27μm.

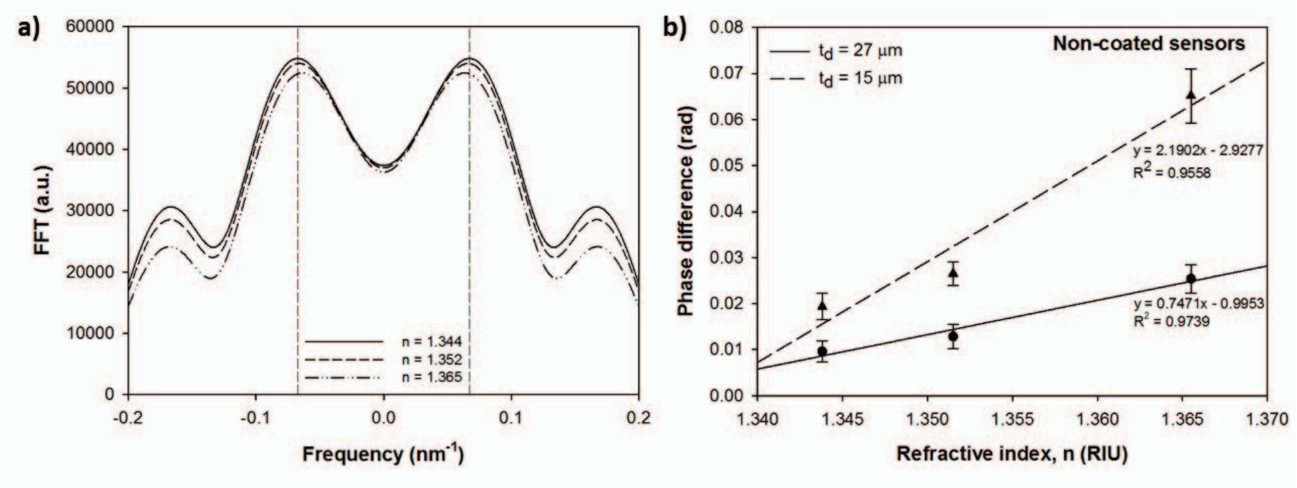

Figure 2: a) Fast Fourier Transform (FFT) of the output fringe patterns in three different iso-propanol solutions.
b) Relationship between phase difference of three iso-propanol solutions and their refractive index for the Fabry-Pérot based sensors with end cap (diaphragm) thickness of 15μm and 27 μm.

Figure 2b) shows the difference in sensitivity of two sensors with end cap thicknesses of 15μm and 27μm. The two sensitivity values were obtained from a linear regression analysis as 2.1902 and 0.7471 rad/RIU for end cap thicknesses of 15μm and 27μm, respectively. The thinner diaphragm has higher sensitivity because there is a static phase shift caused by the diaphragm and this has an effect on the dynamic phase shift when refractive index is changed on the outside of the diaphragm.

Gold was investigated as a potential candidate material for coating at the tip of the sensor as it is known to have optical interaction with hemoglobin [7-9] and can thus be used to determine the refractive index of blood when combined with the FP sensor of this investigation. An initial comparison between non-coated sensors and gold-coated sensors has been performed in order to investigate the influence of the gold coating on the sensors and the results of this are shown in Figure 3.

From Figure 3, it shows that the application of the gold layer at the tip of the sensor increases the sensitivity of the. The sensitivity values with and without the coating are 2.8309 and 0.7471 rad/RIU, respectively. The resolutions of both non-coated and gold-coated sensors were calculated using standard deviation and its sensitivity. In both cases they show that the sensors are capable of resolving circa 10^{-3} RIU.

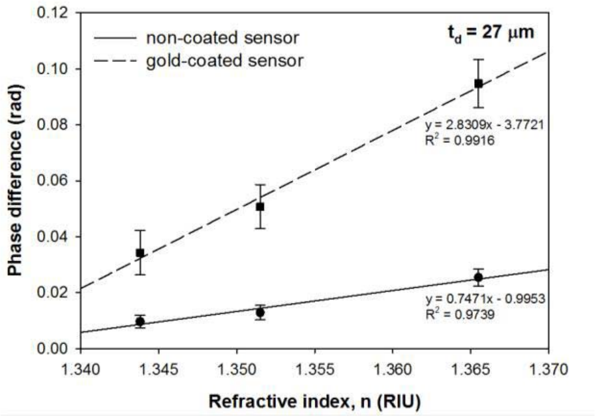

Figure 3: Relationship between phase difference of three iso-propanol solutions and their refractive index for non-coated sensor and gold-coated sensor.

4. CONCLUSION

A Fabry-Pérot based optical fiber sensor for measuring the change in refractive index of biological tissue has been developed and its potential performance evaluated. The sensors have been successfully tested using three different percentage concentrations of iso-propanol aqueous solutions which have refractive index values similar to the range encountered with hemoglobin. The phase variations of the interference pattern from the Fabry-Pérot based sensors were obtained using an in-house developed FFT algorithm. Gold was successfully coated at the tip of the sensors to study a potentially enhanced interaction with hemoglobin. Initial results have indicated a sensitivity of 2.8309 rad/RIU for the coated fiber and 0.7471 rad/RIU for the uncoated version with a baseline resolution of 10^{-3} in both cases. These figures are deemed sufficient to progress the work to further investigation of tissue phantoms and simulated tissue materials. Future work will also concentrate on continuous improvement of the sensor by optimizing the end cap and gold layer thicknesses.

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