

Master in Photonics

MASTER THESIS WORK

**Double Optical Feedback Interferometry for
Biomedical Applications**

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Double optical feedback interferometry for biomedical applications

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Abstract. Optical Feedback Interferometry (OFI) and Double Optical Feedback interferometry (DOFI) are studied as non-invasive techniques for biomedical measurements. Due to its compactness and cost-effectiveness, both sensors provide a very interesting approach for sensing different biomedical parameters. After a brief introduction to the two techniques, a modified signal processing algorithm developed within this MSc Thesis is presented. DOFI is then discussed as a technique for arterial pulse wave shape reconstruction, showing its limitations in large amplitude measurements, which, nevertheless, enable an OFI sensor to accurately measure it. Experimental results on arterial pulse wave measurements will be presented. DOFI is then proposed as a candidate technique for monitoring the displacement of cantilevers in atomic force microscopy which enhances the performance of present cantilever sensing solutions due to its robustness and size.

Keywords: Biomedical engineering, biomedical transducers, non-contact sensors, optical feedback interferometry.

1. Introduction

1.1. Optical Feedback Interferometry and Double Optical Feedback Interferometry

Optical Feedback Interferometry (OFI) has been an active area of research since the early 1980s. This phenomenon was first characterized by Lang and Kobayashi in [1], who analysed the effects of optical feedback in a laser diode (LD) by means of delayed differential equations of the involved electric field. Later models, such as the one presented by Wang [2], use an equivalent two cavity Fabry-Perot (FP) scheme (Figure 1). Under the latter approach the effects of quantities such as the feedback coupling factor (C) and the linewidth enhancement factor (α) over the OFI signal can be analysed once the internal and external cavities are combined into an equivalent cavity, and an analogy with the free-running state laser is established.

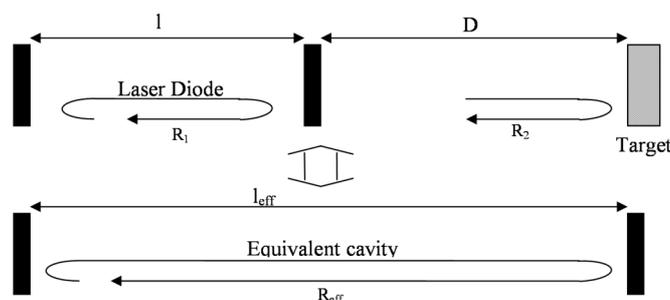


Figure 1. OFI model of internal and external Fabry-Perot laser cavities (up) and equivalent cavity model (down).

From a practical point of view, OFI can be described as the modulation of the laser optical output power (OOP) produced when part of the backscattered light from a moving target re-enters the laser cavity. Depending on the amount of feedback [3], which is accounted by the C value (the coupling factor), the form of the modulation will change, as shown in Figure 2.

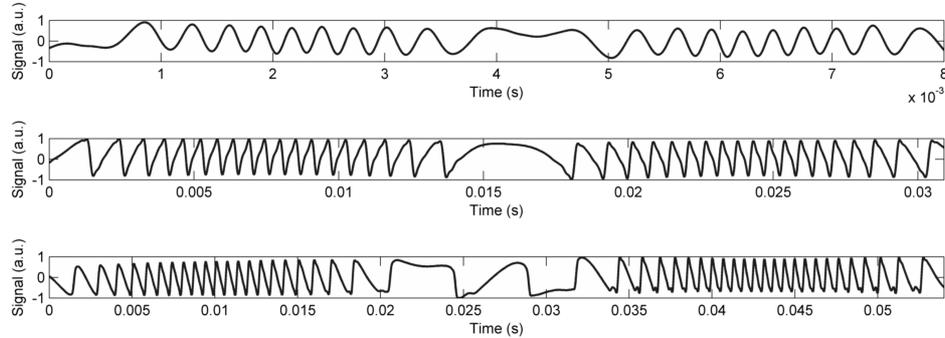


Figure 2. Typical OOPs for a laser under different feedback levels. From top to bottom, OOPs for very weak, weak and moderate feedback regimes.

For values of $C < 0.1$ (very weak regime), very little energy re-enters the laser cavity, and the signal has a pure sinusoidal shape. For values of $0.1 < C < 1$ (weak regime) the signal starts to acquire a sawtooth waveform as the amount of energy re-entering the cavity increases. For $C > 1$ values (moderate regime) the OFI signal becomes sawtooth-like and for large feedback levels it can start to suffer from hysteresis, and present a loss of detectable transitions [4]. At extremely high levels of feedback the OOP enters into a chaotic regime and no information can be extracted. For many OFI applications it is preferred to work within the weak and moderate regimes, since in this type of regions the OFI signal has the best SNR, which enables an easier detection of the transitions in the signal. In this kind of detection each transition is equivalent to a $\lambda/2$ displacement, and the slope of the sawtooth signal enables to infer the direction of the displacement. Although OFI can be generated using different types of lasers, setups usually rely on semiconductor lasers given that it is possible to include a monitor photodiode (PD) in the same package of the LD. With such approach, the LD acts simultaneously as source and detector, avoiding the need for complex alignment procedures, a typical drawback of traditional interferometric setups. The use of this arrangement makes the system extremely robust and compact. Two measurement schemes can be applied in order to recover the OFI signal [5], nevertheless the so called PD scheme discussed here is more general because of its higher sensitivity when compared to the scheme based on the detection of changes in the voltage of the laser junction.

However, the resolution possibilities of this technique rest far away from the ones presented by classical interferometers, where resolutions in the order of a few nanometers can be achieved. The main reason is that OFI is limited to a basic $\lambda/2$ resolution corresponding to the acquisition of a single interferometric fringe. Several efforts in this field have been implemented towards the overcome of this limitation. This limitation in resolution has been broken by Differential Optical Feedback Interferometry (DOFI) [6]. The basic setup for DOFI, shown in Figure 3, involves a measuring laser (L_m) pointing to the target and attached to a motorized linear stage (typically a piezoelectric stage), and a reference laser (L_r) placed at the same distance from L_m to the target while pointing to such motorized stage. A motion of a few micrometers is induced to the platform so that both sensors measure the same reference motion when the target is still. With this approach, even a very small displacement of the target will induce a phase change in the OOP detected by L_m that will allow the reconstruction of the target displacement by differentiating the time elapsed between the transitions in the reference laser and in the measurement laser. This technique achieves a resolution as good as $\lambda/1000$, which is in the order of conventional interferometric techniques but with the advantage of being a low-cost, compact technique where no complex alignment procedures are required.

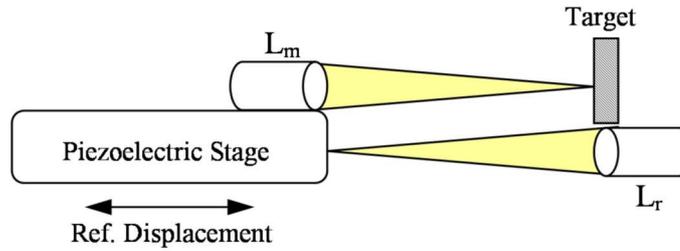


Figure 3. Basic setup of DOFI, consisting of a motorized platform and two laser diodes.

1.2. Signal Processing

The most common way to retrieve the displacement from the OFI (and, subsequently, DOFI) signal is to use the so-called fringe counting algorithm (FCA), which counts the number of transitions obtained in the signal, taking into account the sign of the displacement for each case. As each of the fringes represents a displacement of $\lambda/2$ in a given direction which may be extracted from the slope of the fringe, the displacement can be reconstructed by numerical integration. Most common FCAs use a comparison between predefined threshold levels and the derivative of the OFI signal in order to determine the transitions. This kind of algorithms entails several drawbacks, being the most significant one the possibility of a false detection or a misdetection of fringes. Depending on each case, the threshold level needs to be modified in order to perform a correct detection. The appearance of speckle within the measurements will also affect FCAs since the threshold level should be changed actively throughout the measurement. In the cases concerning this work, typical FCAs cannot be used since the acquired OFI signal and its derivative could not be uniform and different threshold levels need to be defined along the signal to avoid misdetection. In order to solve this problem a modified FCA was developed for this application. The algorithm is based on peak detection and slope comparison to find the position of the fringes. Before starting fringe detection the signal is preprocessed using a low-pass filter to reduce errors in the local maxima and local minima detection due to high frequency components. The proposed method starts by finding all the local peaks (both maxima and minima) in the signal, and storing their positions over a vector. Once the peaks of the signal are detected the algorithm compares the slopes at both sides of each peak, and the largest slope is selected as a transition. Finally, the sign of the transition depends on the position of the higher slope with respect to the peak: if the peak is a maximum and the higher slope is before the peak the transition is positive, in the case of a minimum if the highest slope is before the peak the transition is negative. Some extra steps are implemented to avoid misled fringe detection. The reconstruction is done afterwards by numerical integration. Finally, a low-pass filter can be implemented to smooth the reconstruction. The main advantage of this novel algorithm is that any transition appearing in the signal is correctly detected and in the right position, which was rarely achieved by former algorithms when the target motion has big changes in the direction of the displacement.

2. DOFI in biomedical applications: Pulse measurement

2.1. Background

The characterization of the blood pressure pulse contour has become an essential tool for the assessment of cardiovascular risks. The analysis of the arterial pressure wave shape (APW) and its amplitude provides valuable information about the cardiovascular system [7], which can lead to diagnosis of diseases such as arterial stiffness [8], [9] and arteriosclerosis [10]. The growing interest in this field, related to the increase of cardiovascular diseases around the world, together with the rise of telemedicine practices, requires the development of non-invasive, low-cost, and portable sensors capable of extracting and analyzing the arterial pulse waveform reliably. Therefore, techniques based on optical sensors are an interesting solution for this kind of devices due to the simplicity of their construction, resolution, relatively high bandwidth and low cost.

Two optical methods have proven to be effective solutions for APW characterization: the photoplethysmography method and the laser Doppler method. Photoplethysmography [11] is a technique that recovers the APW by measuring the absorption changes of a defined wavelength due to the variations of the blood volume with each cardiac cycle. Laser Doppler techniques measure the blood flow velocity for a determined time window [12]. By processing several windows and stitching the obtained data, it is possible to estimate the form of the APW.

OFI has been previously used as a non-invasive technique for pulse detection [13], [14] based in laser Doppler. However, this method shows lower resolutions in the reconstruction of the APW shape if compared to photoplethysmography data. Results obtained by OFI in this application are limited to the correlation of the blood pressure measurements using the Doppler spectrogram, rather than to the direct reconstruction of the shape of the cardiovascular pulse.

In this work the DOFI displacement approach was initially proposed in order to recover the APW shape. The cardiovascular pulse can be understood as a pressure wave which produces changes in the radius of the arterial wall and hence a movement on the skin surface. Experiments performed, however, showed the infeasibility of DOFI to measure the APW. DOFI is based on the differences in time of the OOP transitions, and assumes that the reference and the measurement OOPs show the same number of transitions, so a relationship amongst them may be established. However, the movements of the skin induced by the APW have an amplitude of some micrometers, which is greater than $\lambda/2$, so new transitions appear in the measurement signal which were not present in the OOP signal, making impossible an accurate assignment of the fringes between the reference and the measurement signals.

Thus, the classical OFI technique is proposed to measure this movement as it falls within its typical operational range. The results obtained, shown in the next Subsection, show that an approach using the measurement of displacement provides higher accuracy in the reconstruction of the APW than methods based in the laser Doppler spectrogram, comparable to those of photoplethysmographic techniques. In the next section the methodology applied for APW characterization is discussed, as well as the experimental results obtained for the validation of the measurement procedure using a simulated APW on a piezoelectric stage, and then in-vivo measurements showing proper amplitude and frequency measurements of the cardiovascular pulse are presented [15].

2.2. Experimental setup

The LD used to carry out all the measurements is a GaAlAs HL7851G with a nominal output wavelength of 785 nm, and an output power of 50mW. The LD is connected to an amplification circuit and the OFI signal is acquired using a Tektronix DPO2024 oscilloscope. A focusing lens adjusted manually is used in order to control the amount of feedback at different distances from the target.

The OFI signal is generated by pointing the laser beam to any fingernail of the subject to be measured; however, best reconstructions have been obtained pointing at the index or the middle fingers of both hands. The signal can also be recovered measuring directly amplitude changes over the skin, nevertheless, the reconstructed shape is far noisier than the one obtained when measuring at the fingernail. It is also important to notice that over the skin measurements are prone to capture motion artifacts due to involuntary muscle displacements. This problem could be solved by attaching the laser to the finger in such a way that the relative displacement between the finger and the sensor is close to zero. Speckle also plays a relevant role when measurements are performed on the skin. Speckle appears when light coming from a highly coherent source is reflected on a rough surface or on an inhomogeneous medium [16]. Speckle is directly proportional to the surface roughness of the target and the laser spot size, and it is inversely proportional to the distance to the target. Measuring over the nail instead of measuring directly over the skin enhances the signal since the nail has a smoother surface than the skin, therefore reducing speckle noise.

In order to increase the reliability of the measurement, the finger must be in a relaxed state, and as still as possible relative to the laser. To reduce the effects of involuntary tremors over the measurement, it is possible to apply a high-pass filter with a cut-off frequency around 0.5 Hz [17].

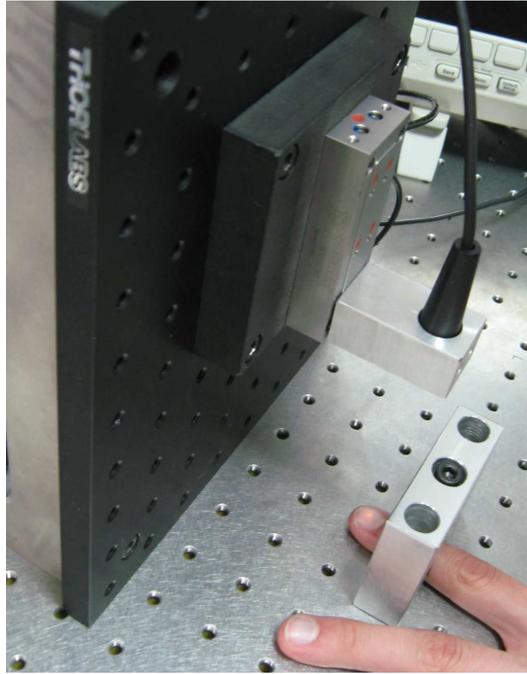


Figure 4. Setup to measure APW with OFI.

The experimental setup used for this work is shown in Figure 4. It uses a simple method to fix the finger to the table top consisting of an aluminum piece with a screw at the top that helps on immobilizing the finger applying a small pressure. The laser head has been attached to a piezoelectric stage in order to set the desired working regime of the laser. To calibrate the working regime it is only necessary to adjust the focusing distance of the laser with the piezoelectric stage turned on and the laser pointing to a fixed target at the measuring distance; the focusing distance is fixed when the sawtooth-like shape is found by looking at the interference signal of a known sinusoidal movement. It is important to set the optimal feedback regime before measuring in order to discriminate the direction of the displacement, which only is possible in the weak and moderate regimes. Another possible scheme to immobilize the finger would be to place a piece with the shape of the finger preventing its lateral movement without the need of mechanical fixation, or clip-based arrangements comparable to those used in photoplethysmography.

2.3. Experimental results

2.3.1. Validation of the procedure.

In order to test possible errors in the pulse form reconstruction or setup, an artificial pulse is generated using a piezoelectric linear displacement stage, and measured and reconstructed using the proposed experimental method. The shape of the generated displacement needs to be as similar as possible to the real pulse shape to be measured in order to be valid. The input signal for the piezoelectric stage is created using the signal generator software. For this study an artificial pulse with $19\mu\text{m}$ peak-to-peak amplitude and 1 Hz was generated. On Figure 5 (top), the superposition between the generated (measured using the capacitive sensor in the piezoelectric stage) and the reconstructed signals using OFI can be appreciated. On Figure 5 (bottom), the error between the generated and the reconstructed signals is shown. It is remarkable to notice that the larger errors correspond to points where there is a large change in slope due to the OOP humps when the direction of the target movement changes, which may produce fringe loss. This defect can be solved using adaptive solutions or using signal processing routines which compensate for fringe loss at these points.

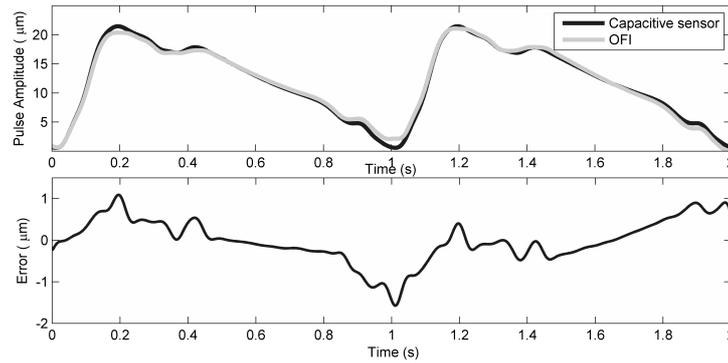


Figure 5. Validation of OFI in APW reconstruction. Measured data is compared with a capacitive sensor located in the piezoelectric stage, which oscillates with a simulated APW shape. The error is obtained as the difference in amplitude of both signals.

2.3.2. *In-vivo* measurements.

Following the former procedure, the measurements have been acquired pointing at the index fingernail of a left hand. In order to ease the signal processing and to reduce errors, the data is acquired when uniformity is observed in the oscilloscope window. The data is then processed in Matlab using the algorithm discussed on Section 1.2.

An example of the typical processed signal and the result of the fringe detection algorithm are shown on Figure 6. It is important to remark that even when a small amount of speckle may be seen it was possible to do the correct detection of all the fringes by using the proposed signal processing algorithm. At first glance, the zones with high positive fringe density correspond with the beginning of the pulse; the lower density zones with negative fringes correspond with the line of descent. If the measurement is performed in moderate feedback regime with the finger at rest, all the fringes appear at the signal and the algorithm is able to reconstruct the signal properly. As shown, reconstructed pulses are well characterized presenting a fast ascent, decreasing to the ‘dicrotic wave’ and finally descending to the base of the next pulse.

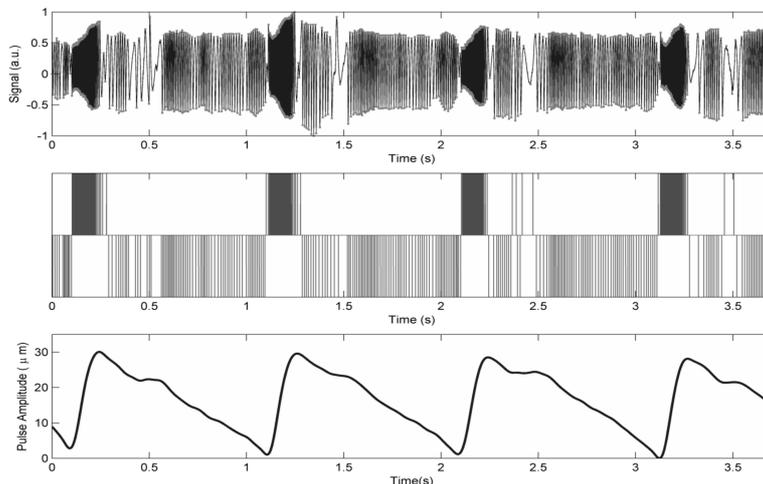


Figure 6. Reconstruction stages of a typical OFI signal obtained in-vivo over the index fingernail. From top to bottom, pre-processed OFI signal, fringe detection, and pulse reconstruction.

By implementing the Fast Fourier Transform (FFT) on the reconstructed APW, the main frequency component of the pulse can be also retrieved with high accuracy. In order to prove that the estimated frequency corresponds to the heart beat rate, a comparison with a heartbeat rate monitor (a commercial sport pulsometer) was performed. In Figure 7, the correlation between the measurement results of both devices is depicted. As it may be observed, both

measurements show a very good agreement, which demonstrates that OFI based methods are extremely valid techniques for the measurement of the heart beat frequency.

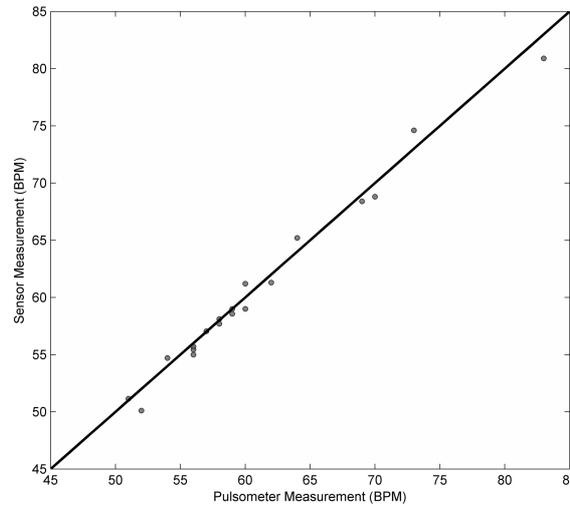


Figure 7. Correlation between pulse-meter and OFI based measurement.

3. DOFI biomedical applications: Atomic Force Microscope Cantilever Monitoring

3.1. Background

Since Atomic Force Microscopy (AFM) was first introduced, it has become an essential technique for a broad range of biophysical applications. The biological applications where this technique extends its domains range from bio-imaging applications, where DNA, proteins, cells and tissues are studied, to the measurement of intermolecular forces or force mapping on living cells [18]. Several techniques have been studied to measure the ultra sensitive interaction between the cantilever probe and the sample, being the most remarkable ones these based on phase shifting interferometry (PSI) and on optical levers [19]. The optical lever technique is the most commonly used for the monitoring of the cantilever response. It uses a laser beam reflected off the cantilever which is detected using either a two-segment or a four-segment photosensitive detector capable of determining the position of the reflected beam. As the cantilever bends, the laser beam changes the direction where it is reflected and then the photodiode produces a measurable voltage that depends on the exact position of the reflected beam. The optical lever method is able to obtain high vertical resolutions in measurement, although it has the drawbacks of being bulky, expensive, fragile, prone to misalignment and not suitable for non-reflective cantilevers. The aim of this work is trying to present the feasibility of DOFI as a robust, compact and precise method for cantilever monitoring in AFM for the implementation of topographic measurements of biological samples.

3.2. Experimental Setup

Two 50mW power LDs are used to monitor the cantilever motion, with measured wavelengths of 773.9nm for L_m and 778.1nm for L_r . Both lasers are connected to independent amplification circuits and the OFI signals are acquired simultaneously using a Tektronix DPO2024 oscilloscope. Each laser has a focusing lens attached in order to control the amount of feedback by changing the focal length.

The experimental setup designed for this work is presented in Figure 8. The reference laser L_r is placed pointing to a piezoelectric stage, P1, while the measuring laser L_m is pointing directly to the cantilever surface and attached to the same piezoelectric stage, P1. The target of the measurement is an AFM cantilever probe, also attached to a piezoelectric stage, P2. The height of the cantilever probe with respect to the sample can be roughly modified by a screw in the support of the cantilever; for finer variations of the height the offset applied to P2 can be used, allowing a vertical movement of 25 μm . The sample to be measured by the AFM probe is

placed over a platform that can be moved in the XY-plane by means of a micrometric platform and a piezoelectric motor.

Transitions in the OFI signals are detected using the signal processing method described in section 1.2 and the time elapsed between transitions in the reference and in the measurement signals are found in order to reconstruct the nanometric displacement of the cantilever. The amplitude of the reference motion will determine the sampling frequency in the reconstruction given that it is a differential technique where the number of samples depends on the number of fringes present in both OOP signals.

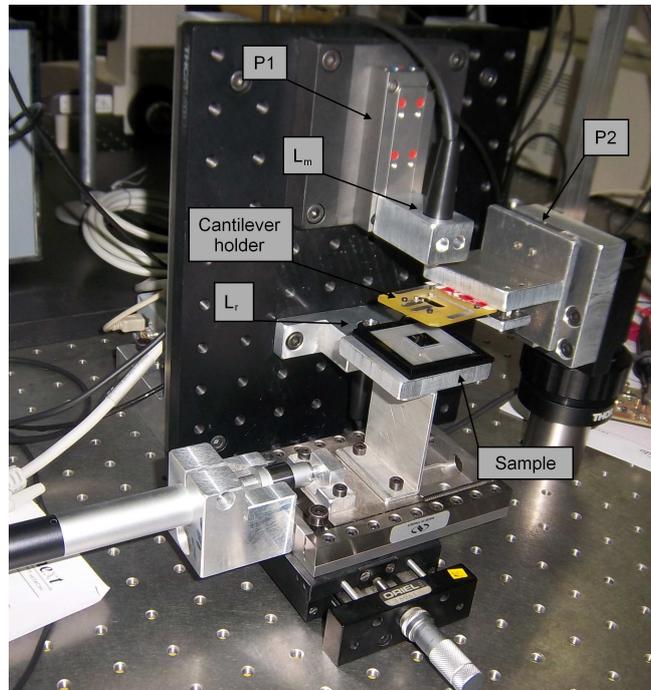


Figure 8. Setup for cantilever monitoring using DOFI.

3.3. Experimental Results

Measurements were acquired applying a ramp signal to the piezoelectric stage P1, with amplitude of $10V_{pp}$ and at different frequencies depending of the sampling frequency desired. Using this amplitude in the piezoelectric stage P1 means a reference motion of $38\mu m$ with constant velocity. To check the noise present in the measurements L_m is focused over the cantilever at rest, obtaining noise levels of about 5nm, as shown in Figure 9. The noise level of the commercial capacitive sensor of the piezoelectric stage which will be used as reference is shown for comparison, and may be seen to be similar to the one obtained with our simple approach. This noise in the measurements is due partly to vibrations of the ground, to little changes in temperature and pressure of air, and to electrical noise and couplings in the wires and circuits of the setup.

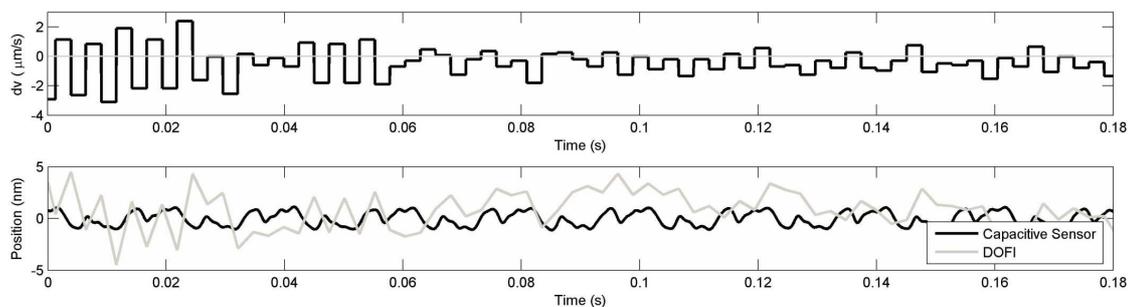


Figure 9. Noise measurement over the cantilever at rest using DOFI and capacitive sensor in the piezoelectric stage.

To monitor the cantilever displacement we apply a sinusoidal vibration of 50nm with a frequency of 25Hz to the piezoelectric stage P2, attached to the cantilever. Focusing L_m just in the surface of the cantilever we were able to reconstruct its motion with high accuracy. In Figure 10 (top) shows the differential velocity calculated between the reference and measured transitions of the OOP signals, in the middle graph the reconstruction of the cantilever motion compared with the one measured at the reference sensor, and at the bottom the absolute error between the measured displacement and the reference. It is noticeable that the order of magnitude of the error corresponds with the noise level measured, which leads to conclude that working on more controlled conditions the error of the measurement could be reduced further.

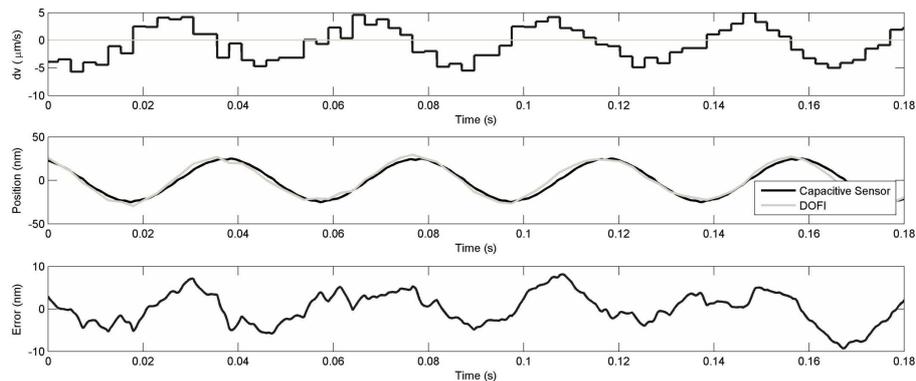


Figure 10. DOFI reconstruction of a 50nm amplitude sinusoidal displacement on the AFM cantilever and absolute error between the original and the monitored displacement using the capacitive sensor.

Measurements have been also performed for 12nm amplitude sinusoidal displacements with a frequency of 25 Hz, where the capacitive sensor is close to its resolution limit. In Figure 11 (middle) the motion reconstruction overlapped to the monitored motion for this case is presented. At Figure 11 (bottom) the absolute error measured between the monitored and the real displacement is depicted, falling again in the noise range.

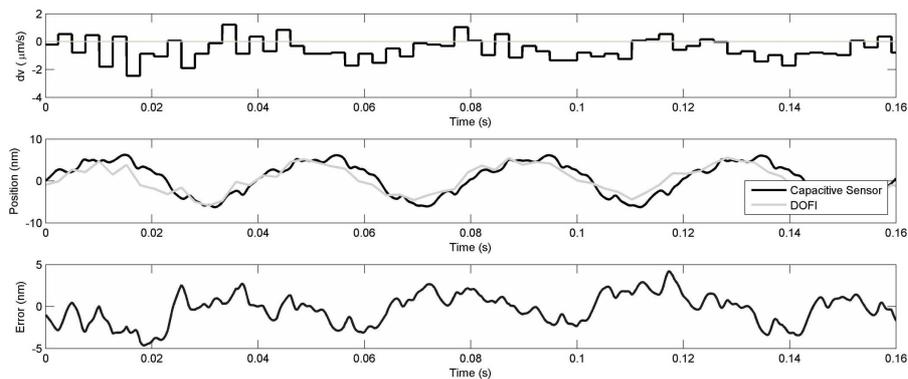


Figure 11. DOFI reconstruction of a 12nm amplitude sinusoidal displacement on the AFM cantilever and absolute error between the original and monitored displacement.

4. Conclusion

DOFI has been studied as a technique for two biomedical applications. Firstly, it has been studied as an APW shape reconstruction technique, evidencing its infeasibility for this kind of applications due to the intrinsic limitations of the technique when displacements over $\lambda/2$ appear in the sample. However, OFI has shown good results for this application using the amplitude measurement approach instead of the classical Doppler-based one. OFI has thus been proved as a simple, low cost and accurate technique capable of measuring the APW shape and heart beat frequency in-vivo and without contact, which can be relevant in intensive care units.

DOFI has also been studied as monitoring technique for the motion of an AFM cantilever, showing its capability to reconstruct sinusoidal displacements with amplitudes of 12nm and 50nm with an accuracy of 5nm under uncontrolled environmental conditions. The error obtained with the technique corresponds to the experimentally measured noise level measured.

Further advances for the pulse measurement sensor will be oriented on developing a sensor able to be directly attached to different parts of the body in order to measure the different APW shapes at concrete points of interest and to the improvement of the algorithm speed for live time pulse measurement. In the case of cantilever displacement monitoring, future research will be oriented on testing the setup under controlled conditions in order to reduce noise level and exploit the full precision of the technique, which theoretically is in the order of $\lambda/1000$.

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