Cavity resonance sensor with disposable analyte container for point of care testing

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***Abstract*—the use of phononic crystals and resonant structures as sensing platforms paves the way to the development of new biomedical technologies. An acoustic sensor with a resonant cavity and a disposable element was investigated in this manuscript. The sensor consists of seven layers with high acoustic impedance mismatch. The disposable element used was a glass spectrophotometry cuvette and, during the experimentation, it was filled with different liquid analytes showing characteristic transmission features that could be used as measures to differentiate and identify them. Experimental transmission curves were obtained using an electronic characterization system that uses a double sideband modulation technique to acquire valuable information about the structure being analyzed. Simulations using the 1D transmission line method were performed to support the experimental realizations. The frequency of maximum transmission has been found to be strongly dependent on the speed of sound of the analyte under test.**

***Index Terms*— Phononic crystals; sensors; biomedical sensor; point of care test; cavity resonance; disposable element;**

I. Introduction

A TROUBLING fact for technological advancement in medicine is that the cost of access to health is constantly increasing and it is becoming more and more difficult for governments to sustain a stable health care system. According to the World Health Organization, WHO, the progress towards the Millennium Development Goals has been slowed down by the lack of low-cost diagnostic systems, and countries with lower economic power have great difficulties in accessing rising technological advances that carry increasingly higher costs. [1]

The development of inexpensive diagnostic systems like point of care tests, PoCT, is one of the most important issues today. This concept is not new, in fact, scientists have been working on PoCT for over 30 years now and a clear example of that is the wide use of PoCT like lactate and glucose test strips all over the globe. [2]

Devices designed for PoCT aim to provide low cost, fast and reliable tests for patients, either at home or in a medical facility, to avoid the need to send samples to specialized laboratories and to be able to make relevant diagnostic decisions at the time of the test, dramatically improving patient care. [3]

Recent advances in biomedical sensing technologies have brought a series of new sensors and applications that could become reliable and inexpensive solutions for PoCT. This might bring significant progress to the practice of medicine and the biomedical industry. The most promising technologies to accomplish this goal are electrochemical, optical and acoustic technologies. [4].

Fundamentals:

Over the past decade, the manipulation of elastic waves has attracted abundant attention to the scientific community. The study of periodic composite materials with wave scattering properties like metamaterials and phononic crystals, PnC, has brought numerous applications that would otherwise be very challenging to realize. Through spatial modulation of its elastic properties, PnC can cause Bragg scattering, giving them the ability to reflect elastic waves at certain frequencies, whatever their polarization and wavevector. The ranges of frequencies in which PnC behave like mirrors, neglecting the propagation of waves, are called band-gaps. [5] [6] Fig. 1 shows a typical 1-D PnC and its respective transmission curve.

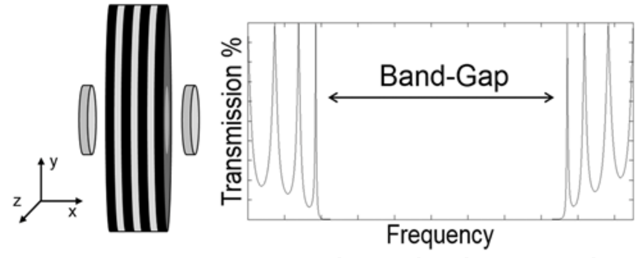


Fig. 1. 1-D PnC representation, gray discs on the sides represent ultrasonic transducers. The graph on the right represents a typical band-gap.

In this manuscript, a phononic crystal based sensor with cavity resonance and a disposable element for biomedical applications like point of care testing is presented.

Phononic crystals have proven to be particularly useful in many applications like acoustic filtering, waveguiding, multiplexing, demultiplexing, super lenses, acoustic cloaking, thermal conductivity and heat capacity control. [7]

The selectivity present in PnC leads to the formation of band-gaps. Studies have found that the appearance of this forbidden bands depends on the elastic parameters of the constituent materials and the geometry of the structure. Density and speed of sound have proven to be the most relevant parameters in order to create complete band-gaps. [5] [6]

Recently, the introduction of defects into the periodic structure has been used to create defect states. These are localized modes that allow the PnC to have transmission bands with frequencies inside the band-gap. This distinctive characteristic paves the way for the creation of high-quality frequency filters, multiplexers and demultiplexers. The properties of the transmission bands, generated inside the band gap, depend on the defect state which enabled their appearance, therefore, any variation in the elastic properties of the defect could generate alterations in the frequency and amplitude of these transmission bands. This feature has been exploited to prove the potential use of phononic crystals as sensors and a few authors have already made some research on this matter and given proof of concept and even proposed an application where phononic crystals could be used as liquid sensors. [8] [9]

When acoustic waves travel through liquids, they induce a series of perturbations, altering the equilibrium and causing a characteristic sound absorption and velocity dispersion. Attenuation and speed of sound measurements deliver valuable information about thermodynamic and kinetic parameters of liquids, this information is often challenging to acquire by other methods. Although these measurement techniques are relatively easy to implement at macro-scale, they are rather challenging in applications requiring micro-scale measurements. It is hard to implement these techniques in micro-fluidic devices because the propagation path of the acoustic waves is not long enough to facilitate the measurements. [9]

With frequencies in the range of MHz, PnC can be assembled in macroscopic dimensions making the use of liquids as constituent materials feasible and opening the possibility of the fabrication of solid-liquid PnC and, therefore, enabling the design of PnC liquid sensors. Changes in the liquids produce displacements in frequency and variations in the magnitude of the transmission, which can be measured with adequate electronics like vector network analyzers and high-frequency lock-in amplifiers. [10][11][12]

The measures of interest in phononic crystal sensors are similar to those on microacoustic sensors: the frequency of maximum transmission, the peak amplitude and the peak band width, taken as full span at half peak value. The approach presented in this manuscript is based on the measurement of the frequency of maximum transmission and the optimization of the peak band width.

II. Materials and Methods

The structure studied in this manuscript consists of 7 consecutive layers with high acoustic impedance mismatch. Material properties, such as thickness, density and speed of sound of each layer of the structure were carefully selected in order to obtain the desired frequency response and be able to quantify changes in the liquid under test.

The designed structure was investigated both theoretically and experimentally to observe its performance and usage as a liquid sensor.

A. Materials

When designing sensors for PoCT, it is important to take into account that all the components that are in contact with the analyte must be disposable. The designed sensor uses a disposable analyte container, a glass spectrophotometry cuvette, which is inserted in the structure and is then discarded after the test. The analyte container is made of glass, which is FDA approved, and the acoustic waves travel through the glass cuvette, as shown in Fig. 2 and generate a liquid cavity resonance that can be measured and characterized to be used for sensor purposes.

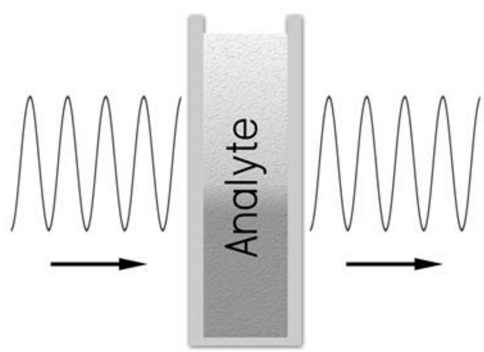


Fig. 2. Representation of a glass cuvette filled with a liquid analyte and the acoustic wave path.

The analyte container is responsible for the generation of the cavity resonance and the main resonance peak is positioned at the desired frequency by adjusting its properties. The impedance mismatch between the cavity walls and the liquid confined inside must be high in order to generate a resonance with a good half-peak band width. Available spectrophotometry cuvettes are made from high-density glass and, therefore, give a good impedance contrast compared with the acoustic impedance of distilled water. Although glass may not have one of the highest acoustic impedances amongst common solids, its cost and easy manipulation make it a good choice to develop point of care sensors.

With a central frequency around 1.05 MHz and the materials of the cavity, high-density glass, the next step is to calculate the layer thickness of the liquid contained in the cavity, d_T. In order to achieve maximum transmission through the layer, its thickness must be equal to a factor of the wavelength, λ, divided by 2. [13] [14]

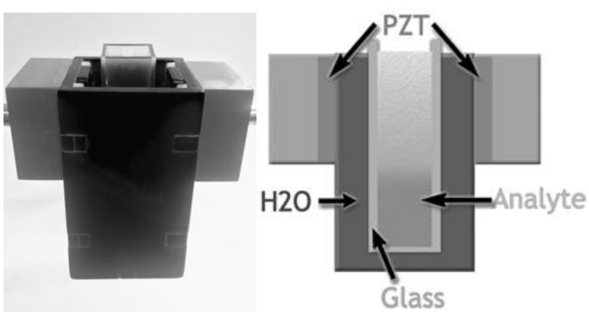
$$d_T = \frac{n\lambda}{2}\ ;\ f = \frac{c}{\lambda}\ \therefore\ f = \frac{nc}{2d_T}\ \therefore\ d_T = \frac{n(1483m/s)}{2(1.05MHz)} = n0.706\,mm \tag{1}$$

The thickness of the walls of the cavity, da, is calculated to have a perfect coupling without losses. This can be achieved having a layer thickness equal to a factor of the wavelength, λ, divided by 4. [13] [14]

$$d_a = \frac{n\lambda}{4}\ ;\ f = \frac{c}{\lambda}\ \therefore\ f = \frac{nc}{4d_a}\ \therefore\ d_a = \frac{(4000m/s)}{4(1.05MHz)} = n0.952mm \tag{2}$$

The most impressing feature of PnC is the formation of band-gaps, the inclusion of this feature in sensing systems can increase the peak half band width of the relevant transmission peaks. The dimensions of the layers of the band-gap are calculated the same way as the thickness of the cavity walls, using a layer thickness of a quarter of the wavelength. The more layers the better the band-gap but the lower the transmission amplitude due to losses in the structure.

The fabricated structure (a) and its graphic representation (b) are shown in Fig. 3. The design was made using a factor of 14 in the thickness of the analyte layer to be able to use commercial spectrophotometry cuvettes, which have a 10mm wide analyte layer.



(a) (b)

Fig. 3. Fabricated Structure (a) with the glass cuvette in the middle and the ultrasonic transducers on each side and its respective graphic representation (b).

The information and details of the materials and layers composing the phononic crystal structure are summarized in Table 1.

TABLE I.
DESIGNED STRUCTURE PROPERTIES

Acoustic Properties				
Layer #	***Thickness mm***	***Material***	***ρ (Kg/m³)***	***c (m/s)***
1	1	PZT	3333	7500
2	10	Water	998	1493
3	1	Glass	3880	4000
4	10	Water	998	1493
5	1	Glass	3880	4000
6	10	Water	998	1493
7	1	PZT	3333	7500

B. *Experimental Setup*

Vector network analyzers and high-frequency lock-in amplifiers are typically used as PnC acquisition systems and their high cost and size does not allow their use outside laboratories, making it impossible to use them in PoCT. Therefore, an electronic characterization system based on a high-frequency double sideband modulation with suppressed carrier was used to acquire the experimental data, Fig. 4. By using a special demodulation, this system delivers accurate transmission curves and allows the use of phononic crystals in the field, thus decreasing the high costs associated with more robust devices. [15]

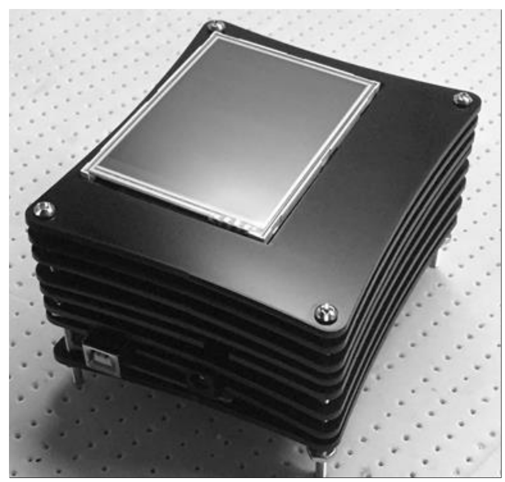


Fig. 4. Electronic characterisation system for measuring frequency changes in phononic crystals.

The number of points acquired with the electronic system was 1000 starting with a frequency of 1.05MHz. The phononic crystal structure was characterized using two ultrasonic transducers having a central frequency of 1.1 MHz and a half-peak band width of 150 KHz. Temperature was kept constant via room temperature control.

Distilled water, ethanol, propanol and commercial milk products were used as analytes. Their acoustic properties are well known and they can give very relevant insights about the performance of the sensor and its potential use in PoCT. The acoustic properties of the materials used as analytes are listed in Table 2.

TABLE 2
PROPERTIES OF THE ANALYTES USED

Analytes		
Material	***ρ (Kg/m3)***	***c (m/s)***
5% n-Propanol solution	992	1520
5% Ethanol solution	996	1514
Distilled Water	998	1493

A total of 3 experimental tests were conducted. All data was acquired using the electronic characterization system previously described. The analyte container was thoroughly rinsed with distilled water and then dried before introducing a new analyte. The temperature was kept constant via room temperature control and all the tests were performed 3 times to corroborate the results. A user interface was developed using the software Matlab® to acquire and process the data from the electronic system.

Characterization of the cavity: The cavity was characterized using the two PZT transducers separated by 10mm to form a liquid cavity with the same dimensions of the one formed with the glass spectrophotometry cuvette. Distilled water and an n-Propanol solution with a concentration of 5% by volumetric fraction were used in this test.

Characterization of the Sensor: The structure designed was characterized using an n-Propanol solution with a concentration of 5% by volumetric fraction and an Ethanol solution with a concentration of 5% by volumetric fraction.

Complex liquids test: the last consisted of using three commercial milk products with unknown properties to observe if the designed sensor could be used to characterize and identify complex liquids in the food industry. The milk products used were lactose-free milk, whole milk and flavored milk.

C. Simulation Setup

Several methods have been developed to simulate the propagation of elastic waves through phononic crystal structures including: the eigenmodes matching theory (EMMT), the transmission line model (TLM), the plane wave expansion method (PWE), the layer multi-scattering theory (LMST), the finite difference time domain (FDTD) and the finite element method (FEM). The FEM is a numerical approach to solve partial differential equations and integral equations, both in the time domain and in the spectral domain. FEM is a powerful method for solving complex phononic crystal structure designs and is capable of delivering accurate displacement field calculations but it has some limitations in computation power and time. [16] [17] [18] [19] [20]

In order to reduce the amount of computation power and time needed to perform the simulations, a 1-D approach based on the transmission line model, TLM, was used. This technique uses an analogy between the propagation of electromagnetic waves and acoustic waves using the similarity between the electrical impedance concept and the acoustic impedance concept. The TLM uses a chain matrix technique and quickly delivers adequate results that allow researchers to understand the behavior of the PnC structure under investigation. The properties of the materials of each layer are used to calculate the elements of the propagation matrix and the transfer matrix. Losses were not considered in the simulations although the TLM could include them in the imaginary part of the acoustic impedance. The use of a 1-D model like the TLM has limitations like lateral miniaturization of the model and focusing of ultrasound into very small volumes, which finally produces results that have some discrepancies with experimental realizations, but, as it has been shown in previous investigations [11, 12, 20], the TLM is very useful to understand the frequency behaviour of the multilayered structures and calculate the frequency displacement of relevant transmission features.

Simulations using the TLM theory were performed to corroborate experimental realizations. The software Matlab was used to run the calculations. The simulations were performed using the same material properties and analytes of the experimental tests and the frequency sweep was done taking the same number of points that were taken with the electronic characterization system, 1000. All the imaginary parts of the acoustic impedance were set to cero, losses were not considered in the simulations. The transmission coefficient was calculated and used for comparing the theoretical results with the experimental results.

The values used for the simulations are listed in Table 3. The values used for the analyte layers are the same values presented in Table 2.

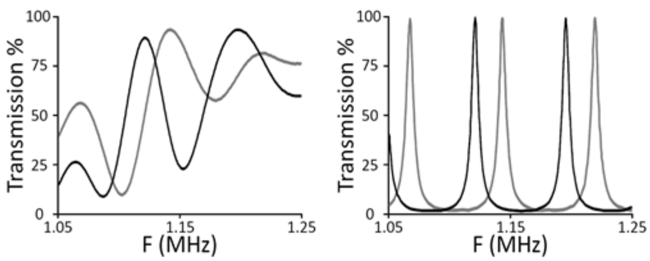
TABLE 3
SIMULATION CONFIGURATION VALUES

Characterization of the cavity				
Layer #	***Thickness mm***	***Material***	***ρ Kg/m³***	***c m/s***
1, 3	1	PZT	3333	7500
2	10	Analyte	-	-
Characterization of the Sensor				
1, 7	1	PZT	3333	7500
2, 6	10	Water	998	1493
3, 5	1	Glass	3880	4000
4	10	Analyte	-	-

III. RESULTS AND DISCUSSION

The first test made was the characterization of the cavity filled with the analyte. Two different analytes were investigated. The acoustic properties of glass and PZT are very different but this test allows to understand the behavior of a cavity with a high impedance mismatch between the liquid contained and the cavity walls. The two analytes used in this first test were distilled water and a solution of n-propanol in distilled water with a concentration of 5% by volume fraction. The results of this first test can be observed in Fig. 5. The simulations were performed using the TLM.

The simulative and experimental transmission curves of the first test agree very well with respect to the frequencies of maximum transmission. The simulative results using the 1-D model have some limitations and do not take into account the frequency response of the ultrasonic transducers, which could explain the differences between simulative and experimental results. The central peak looks very interesting from the sensor point of view because it has the best peak half band width and its frequency of maximum transmission varies with the changes in the acoustic properties of the analyte. Although this arrangement looks very promising, the peak half band width of the experimental results is still too large for sensing purposes.



(a) (b)

Fig. 5. Experimental (a) and simulative (b) results of the test using distilled water and n-propanol. The cavity is filled with an n-propanol solution in distilled water with a concentration of 5% by volumetric fraction (gray) and with distilled water (black).

In order to test the full structure, an experiment using a solution of n-propanol in distilled water with a concentration of 5% by volume fraction and a solution of ethanol in distilled water with the same concentration was conducted.

The results of the simulation using the TLM, doted lines, and the experimental results, solid lines, are presented in Fig. 6.

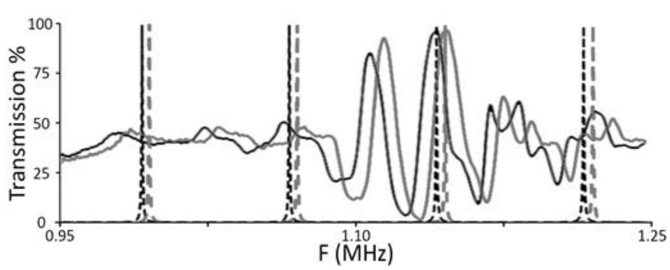


Fig. 6. Experimental (solid lines) and simulative (dotted lines) results of the test using n-propanol and ethanol solutions. The glass cuvette is filled with an n-propanol solution in water with a concentration of 5% by volumetric fraction (gray) and with an ethanol solution in water with a concentration of 5% by volumetric fraction (black). Dotted lines display 1D simulation and the solid lines the experimental results.

The position of the main experimental transmission peaks agree with the 1D simulations, although not all the transmission peaks are covered by the simulations. The final arrangement presents a more complex structure and the lateral miniaturization of the model is no longer valid to present accurate calculations which result in simulations with mayor discrepancies.

The displacement in frequency generated by the changes in the analyte can be easily measured by means of a maximum of transmission, it is clear how the transmission peaks of the n-propanol solution appear at higher frequencies than those of the ethanol solutions due to the difference in acoustic impedance of both solutions.

Fig. 7 shows the comparison between the experimental transmission curves for water in the cavity (black) and the arrangement of 7 layers (gray). The peak half band width decreases considerably with the additional layers increasing the functionality of the system as a point of care sensor.

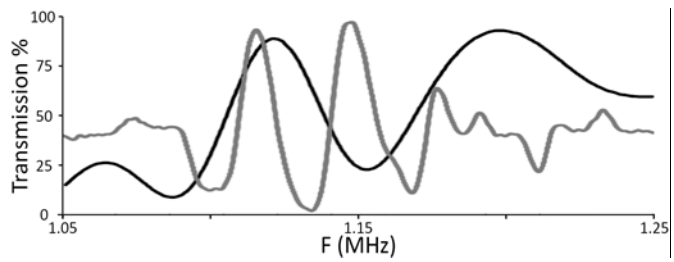


Fig. 7. Comparison between the experimental transmission curves for water in the cavity (black) and the arrangement of 7 layers (gray).

The third test was conducted to analyze if the sensor could be used to characterize or differentiate complex liquids. For this purpose, three commercial milk products of the same brand were used. The first product was whole milk, the second lactose-free milk and the third strawberry flavored milk. The experimental results can be observed in Fig. 8.

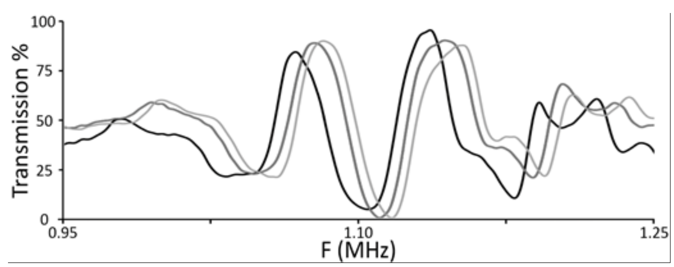


Fig. 8. Experimental results of the tests using commercial milk products. The glass cuvette is filled with whole milk (gray), lactose-free milk (black) and strawberry flavored milk (light gray).

The transmission curves of the three different milk products are well distinguishable and each one of them has transmission peaks with different amplitudes and frequencies that can be used as measures. The flavored milk appears to have its maximum transmission peaks at higher frequencies while the lactose-free milk has its maximum transmission peaks at lower frequencies. The lactose-free milk also shows a different amplitude in both of its main transmission peaks, feature that could be used to differentiate it from the other milk products.

The frequency difference between the whole milk and the lactose-free milk is 3.36 KHz and the frequency difference between whole milk and flavored milk is 2.23 KHz. The results of the third test are very promising because being able to differentiate complex liquids opens the door to the use of this sensor in biomedical applications.

IV. Conclusion

A cavity resonance phononic crystal sensor with a disposable element that is able to quantify differences between alcohol solutions and complex fluids like milk was developed.

The use of a disposable element and the fact that it is fabricated using approved materials opens the door to the possibility of using this kind of sensors in biomedical applications and PoCT.

The experimental investigations show that the use of the 7 layered structure enhances the peak half band width of the resonance induced by the cavity and that changes in the acoustic properties of the liquid confined in it generate displacements in the central frequency of these maximums of transmission.

Although the use of a 1D model to simulate phononic crystals may not present very accurate results due to the obvious limitations, including lateral miniaturization of the model and focusing of ultrasound into very small volumes, it showed to be suitable for designing and understanding the behavior of the phononic crystal sensor.

The sensor design has large capabilities for optimization given the flexibility and robustness of phononic crystals and it enables to adapt the whole system to a large number of applications where the real-time measurement of liquid samples in the field is required.

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