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Executive Summary of the Thesis

Study on the mechanical anisotropy of soft tissues by optical elastography

Laurea Magistrale in Biomedical Engineering - Ingegneria Biomedica

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1. Introduction

Elastography is the cartography of viscoelastic properties of matter. Used on biological tissues, it can be seen as a quantitative palpation examination. Shear waves are elastic waves propagating by transverse deformation of the matter. The speed of their propagation is highly dependant on the elasticity of the media. The stiffer the matter, the faster the shear waves. By propagating shear waves in biological tissue and imaging their propagation, is possible to recover elasticity of the matter. This principle, called shear waves elastography [4] is the core of clinical applications in day by day use. For instance, elasticity of the liver is used to diagnose Cirrhosis, elasticity map are superposed to sonograms delivered by ultrasound systems for the diagnosis of breast cancer.

Most of biological tissues (muscles, skin, brain, etc.) are layered tissues, anisotropically structured. This kind of structure induces a mechanical anisotropy leading to different elastic and viscous modulus according to the direction of the stimulus. Muscles were demonstrated to exhibit high mechanical anisotropy both by ultrasound and MRI. Mechanical anisotropy properties were found on the kidney , with ultrasound system elastography. Mechanical anisotropy of brain tissue was demonstrated through MRI. Breast lesion anisotropy is also under study for tumor detection. Skeletal muscle was proven to be a good indiator of muscles necrosis . Brain's anisotropy properties are directly related to neuropathologies like edema, ischemia or aging (still under study). Kidney anisotropy was detected as a confounding factor for linking kidney's elasticity with kidney's fibrosis.

Gold standard method for elasticity retrieval of matter is the so called *time of flight method*. A burst of shear wave is generated in the matter. The wave front is detected by an imaging device (Ultrasound system, MRI, Optic set-ups, etc.). The tracking of the waves front gives the velocity of shear waves, that is further linked to elasticity. In the 2000's a novel method, called *noise correlation method* derived from seismology was applied for elastographic purposes. From a diffuse field of mechanical waves, for each spatial point, the temporal correlation of the field is computed, providing a description as the time reversed field, is possible to retrieve

the local velocity of shear waves. Once the shear waves speed is known, the elasticity of the tissue can be retrieved. This method strength is twofold. First, it requires a diffuse field of elastic waves. In the human body, elastic waves are travelling due to homeostasis, heart beating, respiration, gastro-intestinal track and more. Those waves are reflected and scattered, leading to a field that can be described as diffused. Noise correlation method can use natural waves present in the body, and do not need any exterior waves generation. It this case it is refered to as *passive elastography*. Second major strengh of this method above the gold standard is its compatibility with slow imaging devices. In fact, shear waves frequency in biological matter require fast imaging techniques to track the waves, on the contrary noise correlation method works even if Shannon criteria of sampling is not met. [1]

The iCube laboratory (Laboratory of Engineering, Computer Science and Imagery - UMR 7357) of Strasbourg where this thesis was conducted is specialized in optical elastography. Optical elastography refers to optic set-ups, mainly digital elastography, optical coherence tomography, Brillouin's microscopy, Laser speckle imaging used in the scope of viscoelasticity properties of matter retrieval [5]. Main benefits of optical elastography techniques are based on the fact that they are non contact techniques and provides high resolution. In the iCube laboratory, it has been demonstrated that using the noise correlation method on diffuse elastic waves field imaged by digital holography, the elasticity of biological tissues can be derived [7].

To our knowledge, the noise correlation method has not been demonstrated to work on anisotropic matter. Furthermore, almost no studies were published on mechanical anisotropy using optical imaging. This work aims at filling those gaps. It provides a way to measure tensor of elasticity in anisotropic soft tissues using the noise correlation method, using finite difference simulations. It applies the presented method on biological phantoms using Laser speckle imaging.

Laser speckle imaging is chosen for its resolution, real time measure, low post processing treatment, above all it's low cost and easy of use. Laser speckle imaging elastography has been demonstrated to successfully retrieve both elasticity and viscosity of biological tissues. [2]

Measuring the mechanical anisotropy of biological tissues using noise correlation technique by Laser Speckle Imaging elastography offers numerous advantages. To summarize, this technique it's usable in vivo to retrieve anisotropy factor and elasticity of the matter with a high resolution and is provided in real time with an impressively cheap and simple set-up. Implemented in an endoscope or used during open surgery this technique could provide a very accessible, low risk, real time elasticity measurement tool.

2. Finite difference simulations of elastic waves

2.1. Elastic waves propagation in isotropic soft solids

Let's consider an isotropic, homogenous, purely elastic solid of volumic mass ρ. It can be described using only two parameters, the Lamé constants λ, μ. Two waves are propagating in the solid, one propagates by deforming matter longitudinally (see figure 1, A), the compression wave, one propagates by deforming matter transversally, the shear wave (see figure 1, B).

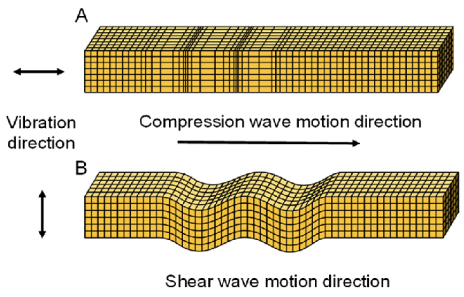


Figure 1: Shear and compression waves propagation [3]

Those two waves propagate independently following wave equation of Alembert's form (equation 1) where 'u' is the displacements, 'c' the wave velocity and 's(t)' the excitation sources.

$$\frac{\partial^2 u}{\partial t^2} - c^2 \Delta u = s(t) \quad (1)$$

In soft mediums, velocity of bulk wave is far above velocity of shear wave $V_L \approx 1500m/s$, $V_T \approx 10m/s$. At the same frequency the wavelength of longitudinal wave is approximately 150 times the wavelength of shear wave. On the scale of shear wavelength only shear waves are able to propagate in the tissue. Therefore, the finite differences simulation (FDM) will only compute shear waves propagation.

According to Taylor's formula, for small displacements variation, we can discretize the wave equation 1. Rest initial conditions are chosen. Boundaries conditions are chosen absorbant. At each iteration, waves sources are applied in specific points of the mesh. The goal is to simulate a diffuse field of displacement, broadband in frequency. To do it, sources are chosen with a white spectrum on a given frequency interval.

2.2. Elastic waves propagation in anisotropic soft solids

Due to their high stratification, biological tissues often present an axial symmetry. Muscle for exemple present an axial symmetry at any plane of their fibers, and a rotation symmetry around the axis of the fibers. As the aim of elastography is to map biological tissues, is important to focus our developements on this type of symmetry called transverse isotropic. For this specific configuration,it can be demonstrated that the equation of propagation allows 3 solutions with distinct phases velocities and polarizations. In the case of digital holography measurement, or laser speckle imaging the displacements measured are only displacements through the normal of the plane direction. It can demonstrated that the technique acts as a filter for the pure transverse waves. Only the pure tranverse waves will be detected and measured. Considering a plane of harmonic wave propagating with purely transverse polarization, the following phases velocities (equation 2) can be retrieved, with θ, being the angle of the propagation with respect to the fibers, $mu_\perp$ the shear modulus normal to the fiber and $\mu_\parallel$ the shear modulus parralel to the fiber. Phase velocities describe an ellipse in the plane of the fibers with a maxima in the direction of the fibers and a minima in the direction normal of the fibers.

$$\rho v_\phi^2 = \mu_\perp sin(\theta)^2 + \mu_\parallel cos(\theta)^2 \quad (2)$$

The propagation is ruled by equation 3. Again, according to Taylor's formula, for small displacements variation, one can discretize this wave equation and simulate the propagation providing initialization and proper boundary conditions.

$$\rho \frac{\partial^2 u_T}{\partial t^2} - \frac{\mu_\parallel}{\rho} \frac{\partial^2 u_T}{\partial x^2} - \frac{\mu_\perp}{\rho} \frac{\partial^2 u_T}{\partial z^2} = 0 \quad (3)$$

2.3. Noise correlation method in a glance

To recover local waves speed, noise correlation algorithm aims to compute local correlation of the wave field. Through an interpretation of the correlation as the point spread fonction (PSF) of the media in this point, and an analogy with time reversal field, it's possible to retrieve the shear waves velocity in the point of interest.
The correlation of the field for $\tau = 0s$ is interpreted as the point spread funtion (PSF) equivalently the focal spot of the wave field in this point. With analogy to the diffraction process, there is a link between the radius of the focal spot (r_0), the wavelength of waves in the media 4, and the numerical aperture of the wave field. Then, by knowing the central frequency of the field (f_0), the velocity of shear waves can be retrieved $c = \lambda f_0$.

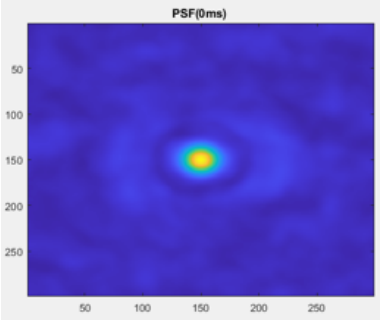
$$a \approx \frac{\lambda}{\alpha} \quad (4)$$

2.4. Noise correlation method and anisotropic media, finite difference simulations

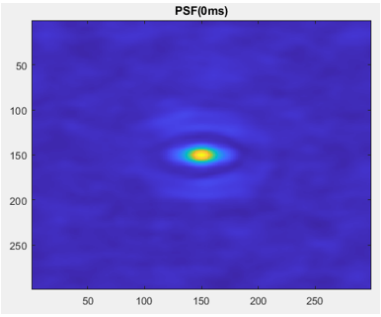
Under the assumption of an isotropic excitation, the correlation's shape is a circle in isotropic media (case (a)), an elongated ellipse for an anisotropic media(case (b)). It's then possible to recover speeds and elasticities in differents directions of propagation. The large axes direction of the ellipse will correspond to the high speed direction. Velocity measurement is based on the shape of the point spread function. A straightfoward idea to distinguish between

isotropic and anisotropic media is to draw their PSF, a circular PSF correspond to isotropic media and elliptic one to an anisotropic media. However, the correlation of an isotropic media with anisotropic distribution of the excitation sources will be an ellipse as well (case (c)), even tough the media is perfectly isotropic. The shape criteria isn't robust enough.
Furthermore, in this specific case the correlation at $\tau = 0s$ is not exactly the point spread function, but is biaised by the source distribution.

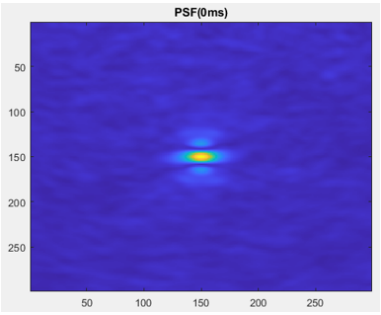
As in experimental condition the repartition of the excitation sources is not always isotropic, the shape of the PSF criteria is not robust enough to drive conclusions on the anisotropy properties of a tissue. Before driving any conclusion on anisotropic samples using the noise correlation method, one should be able to discard the case of an anisotropic distribution of the excitations sources. To do it, we present a classification algorithm able to distinguish between an isotropic tissue, an anisotropic tissue and an anisotropic distribution of the excitation sources.



(a) Isotropic tissue



(b) anisotropic tissue



(c) anisotropic distribution of the sources

Figure 2: Correlation for $\tau = 0s$ simulations in the three cases of interest

3. Classification solver

To obtain a designation of our matter, the development of a classification algorithm is proposed to be able to distinguish between an isotropic tissue, an anisotropic tissue and an anisotropic distribution of the excitation sources. Using the proposed algorithm, is possible to discard the error case of an anisotropic distribution of sources and be able to use the noise correlation method on anisotropic samples. The algorithm takes as input the correlation of the field for $\tau = 0s$ and the correlation of the field during propagation. for the experiment, a decision tree approach with 3 indexes is used, the indexes are: the energy distribution criteria, the ellipse crite-

ria and the axial symmetry criteria. The indexes are then compared to thresholds defined with a trial an error approach on decreasing signal to noises ratio.

3.1. Energy distribution criteria

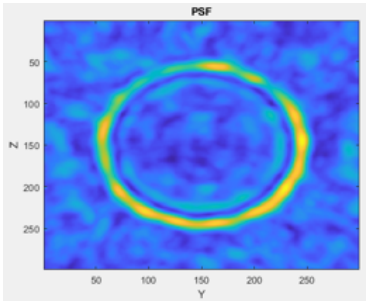
Correlation of the field in the differents cases of interest for $\tau = 150ms$ are displayed in the next page.
If the excitation sources are not isotropically distributed, the energy distribution during the propagation will be anisotropic. In case (b), as there are no sources on the right part of the mesh, no energy is emitted from there. The S index is defined as the variance of the angular energy distribution. Having a large S index means that we are facing an inhomogenous energy distribution during propagation. Therefore, a large S index points on an anisotropic sources distribution.

3.2. Ellipse criteria

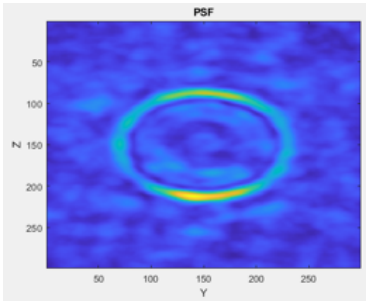
Figure 2 displays the correlation of $\tau = 0s$ for the 3 classes to distinguish. If the media is anisotropic, the correlation will be an ellipse whereas in the isotropic case it will be a circle. To quantify how far an ellise is from a circle, a straightfoward idea is to look at the large and small diameter of the ellipse and to compute their ratios. Calling this ratio 'C', the ellipse criteria defined as the large diameter of the ellipse on the small one.
'C' equals to 1 means that we are facing a circle, therefore, is the case of an isotropic tissue. On the other hand, 'C' < 1 means that we have an ellipse and points to any kind of anisotropy.

3.3. Axial symmetry index

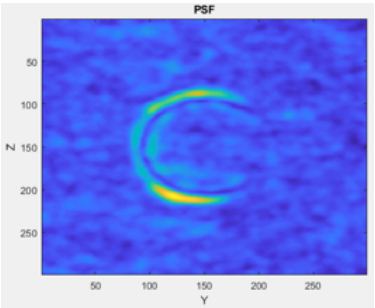
Now, by introducing a new index, 'AS', standing for axial symmetry index. Defined as the upper part on the bottom part times the left part on the right part of the point spread function.
'AS' index indicates if the energy distribution during propagation exhibits an axial symmetry. By this index, is possible to prevent misclassifications of large ellipses with unbalance energy repartition.
The decision tree is proposed in figure 4. The decision tree is then tested on simulations with various parameters and exhibit 100 % of accuracy.



(a) Isotropic distribution of sources, correlation field for $\tau = 150ms$



(b) Anisotropic media, correlation field for $\tau = 150ms$



(c) Anisotropic distribution of sources, no sources on the right border, correlation field for $\tau = 150ms$

Figure 3: Point spread function simulations during propagation in the three cases of interest

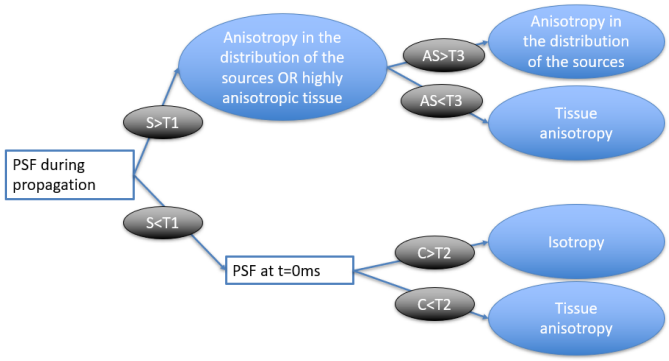


Figure 4: Decision tree for classification, S (symmetry index) , C (ellipse index) , AS (axial symmetry index). T1, T2, T3 are arbitrary thresholds defined by trials and errors on simution of noisy data

4. Laser speckle imaging elastography

Through simulation of elastic waves propagation the following statements have been demonstrated.
First, correlation of a diffuse field of waves allows to retrieve waves velocity in the media and its elasticity.
Second, in mechanically anisotrope media, the mechanical anisotropy ratio can be retrieved, but only if the diffuse field is isotropically distributed around the point of interest.
The case of an anisotrope diffuse field can be detected provided the computation of 3 different indexes and being discarded from other cases.
Waves have been simulated in a 2D plane, displacements are filtrated on the normal axis to the plane, in plane, the displacements are set to 0. The experimental configuration is mirroring the simulation. Indeed, Laser speckle imaging performs a 2D measure of waves propagating with normal polarization with respect to the surface plane. The most important difference is the sample rate. The camera used during the experiment is not fast enough to allow a proper sampling of waves frequency of propagation. To overcome this issue, two concurrent approaches will be used: stromboscopic sampling of impulses and noises correlation.

To provide experimental proof the workflow is described as the following steps:

1. Verify the ability of Laser Speckle Imaging to retrieve with good result the elasticity of Agarose samples using the gold standard method of time of flight. Mechanically isotropic and anisotropic agarose samples will be characterized.
2. Retrieve elasticity of agarose samples using correlation of a diffuse field method, taking as comparison the gold standard method.
3. Underline experimentally the bias in the measured velocities of waves with anisotropic distribution of the diffuse field sources.
4. Show that the previous situation can be detected and then avoid to follow the former proposed decision tree.

For sake of clarity, in the executive summary, only results obtained by noise correlation method are presented.

4.1. Material

4.1.1 Set-up description

The laser used is a semiconductor laser uncollimated of power 82mW. A CMOS camera (Basler aceA2040) of 2048px *1536 px and pixels of 120μm is used with its maximal sampling frequency 112Hz and an exposure time of 200μs. The objective used (Navitar) has a 25mm focal and an aperture of 1.4. To generate shear waves in samples an amplified piezo actuator (Cedrat technologie APA100M-19-008) is driven by a function generator (Tecktromic AFG1062). To generate diffuse wave field piezoelectric patches are used driven by pulse width modulation and an arduino board.

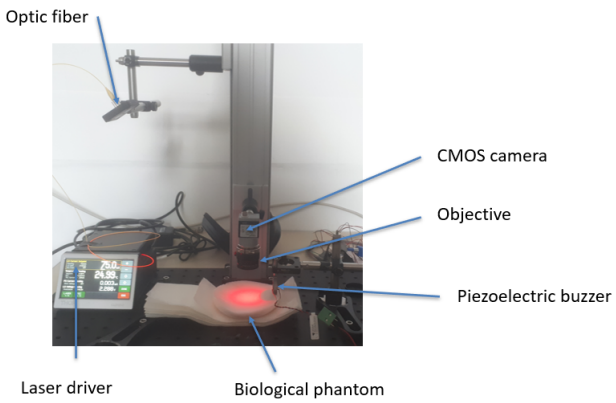


Figure 5: Picture of the set up used in the lab

Picture 5 shows the experimental set-up. Laser

is powered by a laser driver and pass through an optic fiber. The laser beam hits the biological sample with a tilt angle. The speckle pattern is imaged by an objective and registered on a CMOS camera sending data to the computer. Pixels are 28 μm large and the entire field of view is 5.7cm * 4.3cm. The numerical aperture of the objective is set to 1.4, its maximum.

4.1.2 Preparation of samples

Samples are made out of Agarose(A9539, Sigma-Aldrich, St. Louis, Missouri) with mass concentration between 0.5% and 1%, and TiO2 nanoparticles (277370010, Acros Organics, Morris Plains, New Jersey) with mass concentration of 1%. Agarose and water mix were heated under constant agitation then poured into a recipient. The samples were cooled at 4 C° for 1 hour to obtained a solid circular sample of 10cm diameter. Obtained elasticity are between 1 and 100 kPa [6] providing good comparison with biological soft tissues.
Anisotropy in the sample was created using sewing wire. The wire was streched on the recipient before the agarose mix was poured. It was streched in only one direction. Once the sample is cooled, a final layer of agarose is poored and cooled on the surface to make sure the wire is recovered and embedded in the agarose matrix.

4.2. Methods

4.2.1 Processing of raw speckle images

To obtain waves propagation from collected speckle images, two processing steps are applied. First differences of succesive images is performed to obtain a differential stack D (equation 5 with I(n) the nth image acquired).

$$D(n) = I(n+1) - I(n) \tag{5}$$

Second the spatial contrast of each image of the D stack is computed to obtain a differential contrast stack DC. To do so, the local contrast on subregion A of 2x2 px is computed using equation 6 where σ is the variance of the pixels in region A. The resulting convoluted image of spatial contrast is the differential contrast on which the propagation of waves is visible.

$$C[A] = \frac{\sigma(D[A])}{mean(I[A])} \tag{6}$$

4.3. Results and discussions

Noise correlation method is used to retrieve shear waves velocity. Shear waves are send through 8 piezoelectric buzzers placed in fixed position all around the field of view and driven by an arduino board to send a sinusoidal wave at a given frequency.

4.3.1 Isotropic samples

In this section, homogenous, isotropic samples of given percentage of agarose are studied with an isotropic distribution of the diffuse field. The obtained field is retrieved by computation of the differential spatial contrast in time. On the acquired film is possible to qualitatively follow the isotropic propagation of waves front.

The correlation of the field for $\tau = 0s$ is computed and displayed in figure 6. Qualitatively the shape of the focal spot is circular, as expected. From this correlation, velocities of 1 m/s for 1% agarose are retrieved by noise correlation .

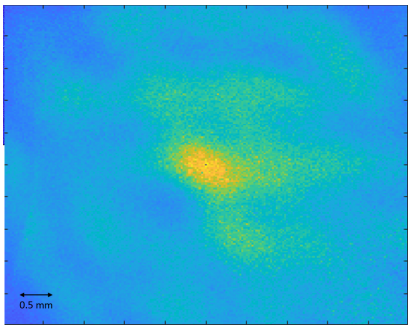


Figure 6: Correlation of the diffuse field for $\tau = 0s$ in an isotropic agarose sample (1% agarose, 1% TiO2) with isotropic distribution of the diffuse field around the field of view.

4.3.2 Anisotropic samples

In this section the samples are anisotropic and are studied with an isotropic distribution of the diffuse field. The samples exhibit different velocities according to their propagation direction with respect to the sewing wire embbeded in the agarose matrix.

To test the different directions, two experiments are conducted for each sample. A

first experiment is done with an isotropic distribution, if the excitation sources, then the sample is turned of 90° degrees and the same acquisition is obtained with the same locations sources.
The obtained fields, are retrieved by computation of the differential spatial contrast in time. Qualitatively the waves front seems to travel up and down for case 1 and side to side for cqse 2. Those observations are in agreement with an anisotropic sample rotated between the two videos.
Correlation of the obtained fields are computed and displayed in figures 7 and 8. Looking at the two correlations, is expected to obtain the same spot with a circular rotation of 90°. Qualitatively, focal spot in figure 8 is much larger than in figure 7. Nevertheless, is possible to notice that the larger dimension happens when the focal spot is rotated 90°. Waves velocities retrieval are around 1 m/s with an anisotropic ratio around 1/2.

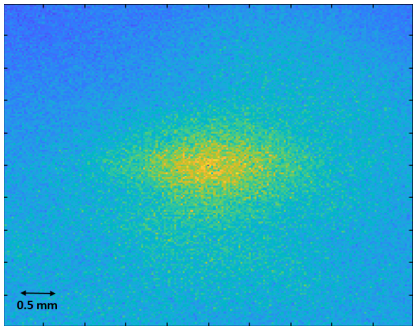


Figure 7: Correlation of the diffuse field for $\tau = 0s$ in an anisotropic agarose sample (1% agarose, 1% TiO2, sewing wire), with isotropic distribution of the diffuse field around the field of view.

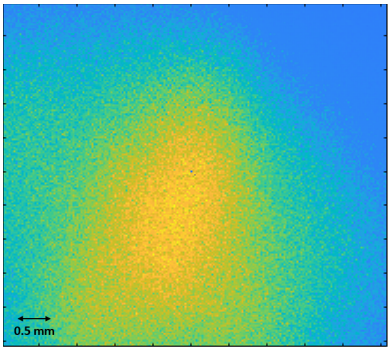


Figure 8: Correlation of the diffuse field for $\tau = 0s$ in an anisotropic agarose sample (1% agarose, 1% TiO2, sewing wire), with isotropic distribution of the diffuse field around the field of view, the sample has been rotated of 90° with respect to figure 7

4.3.3 Anisotropic distribution of the piezo buzzers

In this section samples with constant stiffness are studied with anisotropic distributions of piezoelectric buzzers. The buzzers are only placed on the low half of the sample, outside the field of view. The obtained field is retrieved by computation of the differential spatial contrast in time. On the film of propagations, is possible to qualitatively follow the anisotropic propagation of wave fronts travelling from the bottom to the top of the field of view.

Correlation of the retrieved wave field is computed for $\tau = 0s$ and displayed in figure 9. The shape of the focal spot is elliptic, there is a bias in velocity retrieval.

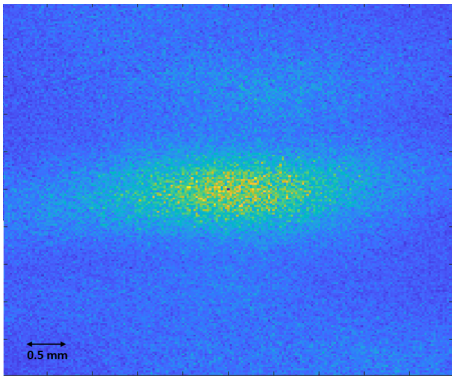


Figure 9: Correlation of the diffuse field for $\tau = 0s$ in an isotropic agarose sample (1% agarose, 1% TiO2) with anisotropic distribution of the diffuse field around the field of view.

5. Conclusions

Mechanical anisotropy of biological tissues is a way to characterize matter and link their results to different pathologies.
Noise correlation method combined with optical elastography allows to have an uncontact retrieval of viscoelastic properties of matter.
In this work, a bias in mechanical anisotropy of matter retrieval by noise correlation is highlighted. Simulation of elastic waves propagation in 2D medium were implemented. A classifier algorithm able to target the situations leading to errors is proposed based on the simulations. Experimental verifications on agarose samples presenting isotropic and anisotropic mechanical properties are performed. Laser speckle imaging is used and proved to bring good results for elastography with the gold standard method of time of flight on stromboscopic data. Laser speckle imaging elastography is then performed on agarose samples with noise correlation method. Preliminary results show good agreement with the gold standard method. Using noise correlation method, a bias in the retrieval of anisotropy of tissue is experimentally highlited .

6. Acknowledgements

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