In vivo measurement of breast tissues stiffness using a light aspiration device

Noémie Briot, Grégory Chagnon, Nathanaël Connesson, Yohan Payan

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N. Briot*[1], G. Chagnon[1], N. Connesson[1], and Y. Payan[1]

[1]Univ. Grenoble Alpes, CNRS, UMR 5525, VetAgro Sup, Grenoble INP, TIMC, 38000 Grenoble, France

* Corresponding autor : noemie.briot@univ-grenoble-alpes.fr

Abstract

Background: This paper addresses the question of the in vivo measurement of breast tissue stiffness, which has been poorly adressed until now, except for elastography imaging which has shown promising results but which is still difficult for clinicians to use on a day-to-day basis. Estimating subject-specific tissue stiffness is indeed a critical area of research due to the development of a large number of Finite Element (FE) breast models for various medical applications.
Methods: This paper proposes to use an original aspiration device, put into contact with breast surface, and to estimate tissue stiffness using an inverse analysis of the aspiration experiment. The method assumes that breast tissue is composed of a bilayered structure made of fatty and fribroglandular tissues (lower layer) superimposed with the skin (upper layer). Young moduli of both layers are therefore estimated based on repeating low intensity suction tests ($< 40mbar$) of breast tissues using cups of 7 different diameters.
Findings: Seven volunteers were involved in this pilot study with average Young moduli of 56.3 kPa ±16.4 and 3.04 kPa ±1.17 respectively for the skin and the fatty and fibroglandular tissue. The measurements were carried out in a reasonable time scale ($< 60min$ in total) without any discomfort perceived by the participants. These encouraging results should be confirmed in a clinical study that will include a much larger number of volunteers and patients.
Keywords: Breast, in vivo stiffness estimation, Young modulus, bilayer structure, Vlastic aspiration device

Introduction

Over the last 20 years, biomechanical Finite Element (FE) modelling of human breast tissues has been investigated for various medical applications such as surgical procedure training (Babarenda Gamage et al., 2019), preoperative planning (Vavourakis et al. (2016); Weis et al. (2017)), clinical biopsy (Tagliabue et al., 2019), image registration (Han et al., 2013), mammography (Chung et al., 2008), or image-guided surgery (Richey et al., 2021). The choice of appropriate constitutive equations associated with each breast tissue has strong consequences on numerical simulations. This was illustrated by Eder and colleagues who tested 12 material properties proposed in the literature to FE simulation models derived from prone MRI breast datasets of 18 female volunteers (Eder et al., 2014). The upright position of the breast was simulated for each model and then compared to the real breast geometry as collected on the volunteers in standing position. Distances between the breast surfaces simulated with various constitutive laws could reach a maximum of 3 cm, which illustrated how the numerical results are sensitive to material properties (Eder et al. (2014) - figure 5).

Most FE models reported in the literature assume constitutive equations estimated from ex vivo experiments (see for example O'Hagan and Samani (2009)) and/or using an optimisation technique to identify the constitutive parameter values that allowed the FE model to reliably predict a number of gravity-loaded configurations of the breast acquired using 3D images (Rajagopal et al., 2008). Some of these constitutive parameters are reported in Gefen and Dilmoney (2007). Measuring the breast constitutive parameters in vivo seems, however, a prerequisite if a subject-specific clinical application based on FE simulations is targeted. The mechanical behaviour of living tissues varies significantly between in vivo and ex vivo conditions, for a number of reasons, including the lack of vascularisation and protein degradation of ex vivo tissues (Gefen and Margulies (2004); Kerdok et al. (2006); Ottensmeyer (2002), Girard et al. (2019)). Moreover, for the same subject, a significant cyclic change in breast tissue elasticity has been demonstrated in phase with the menstrual cycle, with elasticity values that were highest among days 11 and 25 (+35%), and lowest (−29%) on Day 5 after onset of menses (Lorenzen et al., 2003).

Elastography is nowadays a well-established non-invasive technique to estimate in vivo the elasticity of the human breast soft tissues. The underlying idea consists in generating a mechanical wave inside the tissue and measuring the wave propagation speed, which can be related to tissue stiffness (equivalent Young modulus). Clinically available elastography techniques include US-based elastography such as transient elastography (TE) and point shear wave elastography (pSWE), and MR-elastography (MRE). In a recent review paper, Bohte et al. (2018) described current developments in the field of breast MRE and highlighted the variability of subject-specific tissue stiffness estimated from various studies of literature (with, for example, fibroglandular tissue shear moduli ranging between 0.85 and 10.8 kPa and fatty tissue shear moduli ranging between 0.43 and 8.5 kPa (Bohte et al., 2018)). Despite its high potential in the accurate estimation of subject-specific breast tissue stiffness, the MRE technique is still quite far from use in daily clinical practice. US-based elastography such as shear waves elastography has probably an advantage over MRE by means of its availability and its lower cost. However, if we target the estimation of subject-specific breast tissue stiffness for many clinical applications, it might be relevant to propose a much lighter device that would not rely on any imaging modality. This approach has been studied by our group since 2009 using the aspiration technique. Such a technique consists of putting a chamber with an aperture in contact with the investigated tissue and in decreasing the pressure inside the chamber in order to mechanically load and test in suction the investigated zone. Because of the vacuum pressure, the portion of the tissue under the aperture is partially aspirated, with an amount of aspiration related to tissue stiffness. Our group recently proposed to use a light disposable aspiration system reduced to a simple tube with a customisable (in size, shape and material) head aperture, able to meet any required severe sterilisation process (Elahi et al. (2018); Elahi et al. (2019); Connesson et al. (2022) - under review). This method, called VLASTIC, has been validated by comparing its estimations of synthetic material stiffness with the ones measured with classical experimental tensile tests. This was done using homogenous silicone phantoms. Results obtained showed that errors in stiffness estimations remained below 7% (Elahi et al., 2019). The method has been used in a clinical pilot study to measure the tongue stiffness assuming an isotropic homogeneous material for tongue tissue (Kappert et al., 2021).

Recently, the VLASTIC method and device have been developed to address bilayer materials and were tested on bilayer phantoms (Connesson et al. (2022) - under review). The method provided correct stiffness estimation of both layers with the same order of error magnitude (around 15%). The objective of the present paper is to use the bilayer version of the VLASTIC method to estimate the breast tissue stiffness of seven healthy volunteers with measurements made in three regions of the breast. The organ was assumed as a bilayer structure with the top layer representing the skin and the underlying layer approximating the fatty and fibroglandular tissues. The VLASTIC method as well as the experimental set-up for the pilot study is described is Section 1 while Section 2 provides the breast tissue stiffness estimated for each volunteer.

1 Materials and Methods

1.1 VLASTIC method

The VLASTIC device is made of a small syringe used to cyclically withdraw a known volume $V_{syringe}$ (Figure 1 -a-), from a system composed of a manometer, a valve, connection tubes and a 3D printed resin cup of aspiration diameter D_i. This cup rests onto the tested material (breast skin here). The idea consists of measuring the negative pressure P during quasi-static cyclic tests. A parallel calibration procedure is used to evaluate the impact of the deformation of the system during a suction cycle. Different apertures can be used (resin cup of aspiration diameters D_i varying between 4 and 30 mm, Figure 1 -c-).

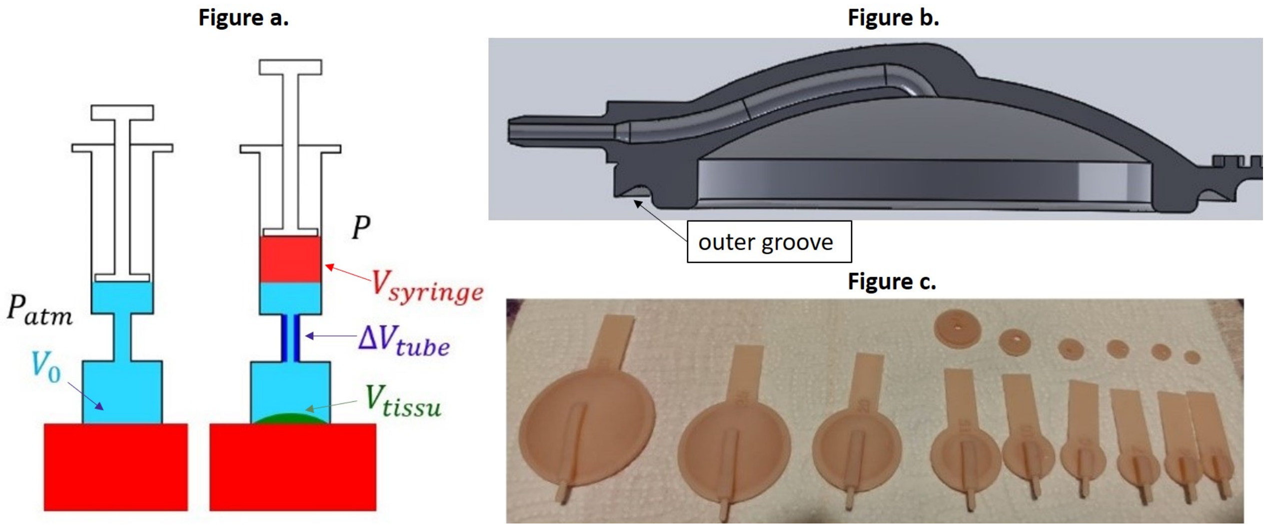

Figure 1: VLASTIC device, with aspiration cups of various diameters; -a- functional sketch of the device -b- cross-section of a cup -c- all the different cup diameters available

Once the Pressure-Tissue Volume curves are collected, an inverse analysis is performed using an axisymmetric Finite Element (FE) model (ANSYS software) to estimate the Young moduli of the bilayer structure (equivalent stiffness in small strains).

Assuming the breast tissue is made of two isotropic homogeneous materials, namely the skin (upper layer) and the fatty and fibroglandular tissues (lower layer), the FE model includes two incompressible Neo–Hookean materials (Treloar (1943); equation (1)) with parameters C_{10Skin} and $C_{10Fat/Gland}$ (thus providing the equivalent Young moduli E_{Skin} and $E_{Fat/Gland}$ with $E = 6C_{10}$ in the framework of the quasi-incompressibility hypothesis). The calibration of the material parameters using the inverse analysis only concerns the coefficients of the bilayer structure material constitutive equation:

$$W_{Neo} = C_{10}(I_1 - 3) \quad (1)$$

The skin thickness is given as a parameter of the FE model and is measured by US echography.

1.2 Experimental Protocol

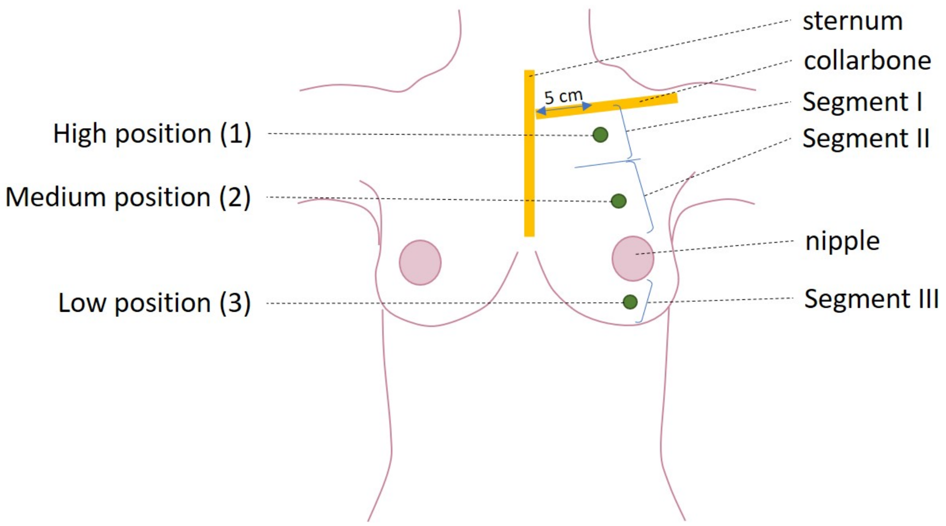

Figure 2: Cups positions defined by anatomical markers

Seven healthy women (age between 19 and 55 years old, BMI between 20.3 and $24.8 kg/m^2$, bra cup between A and D) gave their informed consent to the experimental protocol of this pilot study, as required by the Helsinki declaration (1964) and the local Ethics Committee (study agreement CERNI N° 2013-11-19-30). Three breast anatomical positions (high (1), medium (2) and low (3)) were tested on each volunteer (see Figure 2). Seven cups with various diameters (4-6-8-10-12.5-15-20 mm) were used with subjects lying on a table in supine position. Subjects were requested to stay calm with a normal breathing, without talking during the measurements (the VLASTIC measurements are sensitive to any vibrations due to speech). Four successive measurements comprising each five aspiration cycles were collected for each position on the breast (the three positions being marked with a pencil cross).

During each measurement, the cups were carefully placed on the position markers. To prevent air leakage, ultrasound gel was put in the outer groove of the cup (visible in the cross-sectional view in Figure 1 -b-) before applied onto the skin. Special care was taken to ensure that the gel does not get inside the cup. The cup was held in position using medical plasters placed at both ends of the cup as shown in Figure 3. The plasters did not press on the cup and were only used to hold it in position. Once the tests had been carried out, the cup could be easily removed and the same protocol was applied for the next cup diameter.

2 Results

2.1 Skin thickness measurement through ultrasound

In order to estimate the Young modulus values of the two layers, it is necessary to know the thickness of the upper layer i.e. skin thickness here (the lower layer being considered infinitely thick). To achieve this, five ultrasound measurements (as shown in Figure 4) were carried out for each position on all the volunteers. The measurements were accurate to $\pm 0.1 mm$ (precision given by the ultrasound device).

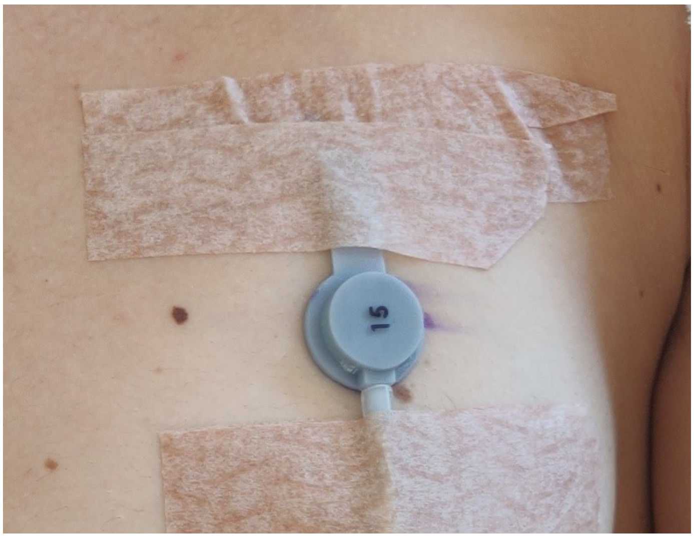

Figure 3: 15 mm VLASTIC aspiration cup during measurement in position 1

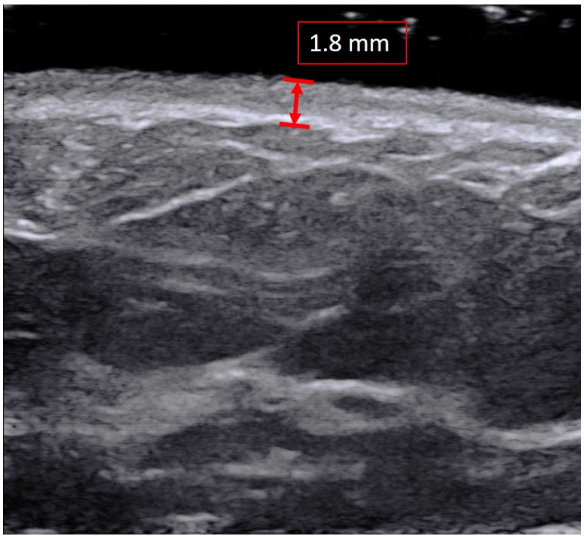

Figure 4: Ultrasound measurement of skin thickness (upper layer)

Table 1 lists the skin thicknesses measured on the seven volunteers.

Volunteer	**Skin thickness [mm]**		
	Position 1	**Position 2**	**Position 3**
1	1.2	1.7	1.8
2	1.4	1.7	1.4
3	1.7	1.7	2.1
4	1.8	2.0	1.7
5	2.1	2.3	2.5
6	2.0	2.2	2.4
7	1.7	1.7	1.4

Table 1: Skin thickness (upper layer) measurements on all volunteers

2.2 Estimations of skin and fibroglandular tissue stiffness

For each volunteer, all seven cups are used in each of the three positions. For each cup, a series of 5 suction cycles is performed. Figure 5 plots all the pressure-volume cycles performed for the seven cups in one position.

A linear regression line of the Pressure/Volume curves is then modelled to approximate the apparent stiffness $\Delta P/\Delta V$ for each cup.

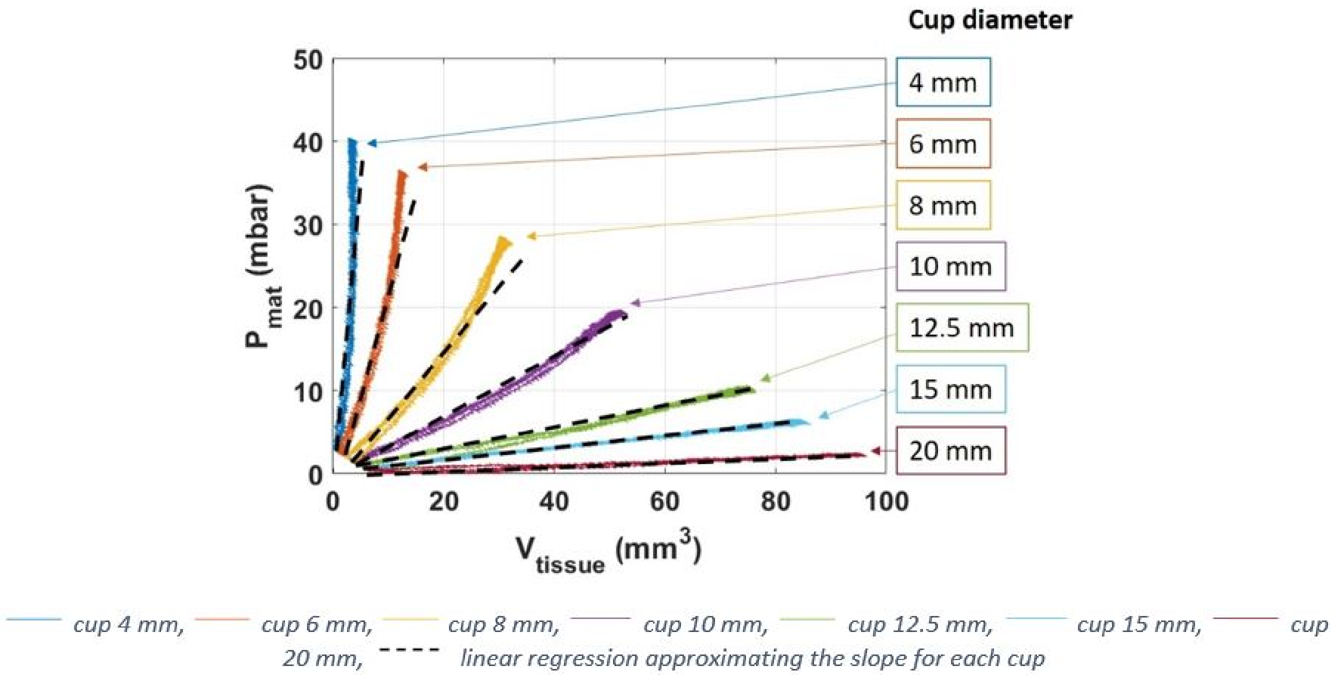

Figure 5: Pressures measured as a function of the volume of material sucked in for the seven cups at position 2 of volunteer 6

The cycles are very reproducible and a clear difference between cups is observed. Figure 6 plots, for each cup (colour points), the apparent stiffness $\Delta P/\Delta V$ estimated by the linear regression taking all the curves in consideration.

An axisymmetric Finite Element model of the suction experiment is built (Figure 7), in order to estimate the Young modulus of each layer of these sets of discrete measurements of apparent stiffness (colour points on Figure 6). In practice, the optimisation process reduces CPU time by using a pre-calculated FE database gathering models and results created for specific ratio of layer thickness over cup sizes. The Young moduli of skin and fibroglandular tissue layers are optimised to best fit the experimental points, resulting into the blue curve in Figure 6 (drawn for any cup size).

The Young moduli of skin and fibroglandular tissue obtained for the seven volunteers are shown in Table 2. A clear difference is observed between the moduli of the upper and lower layers. The average Young modulus of the upper layer is 56.3 kPa while the average for the lower layer is 3.04 kPa, with respective standard deviations of 16.4 and 1.17 kPa.

Connesson et al. (2022) (under revision) implemented a method based on indifference regions to quantify the uncertainty zone at 95% for each estimation of the Young modulus. Figure 8 plots the Young moduli estimated from measurements of all volunteers for each of the 3 positions with the corresponding uncertainty zones.

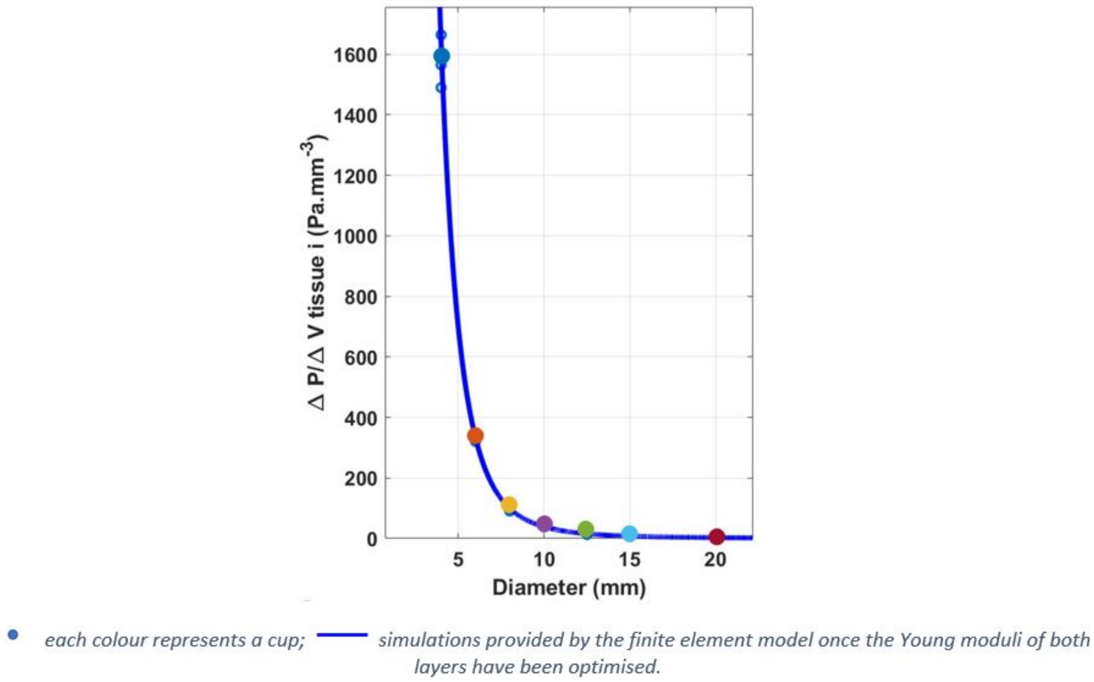

Figure 6: Apparent stiffness $\Delta P/\Delta V$ estimated for each cup on the positioin 2 of volunteer 6

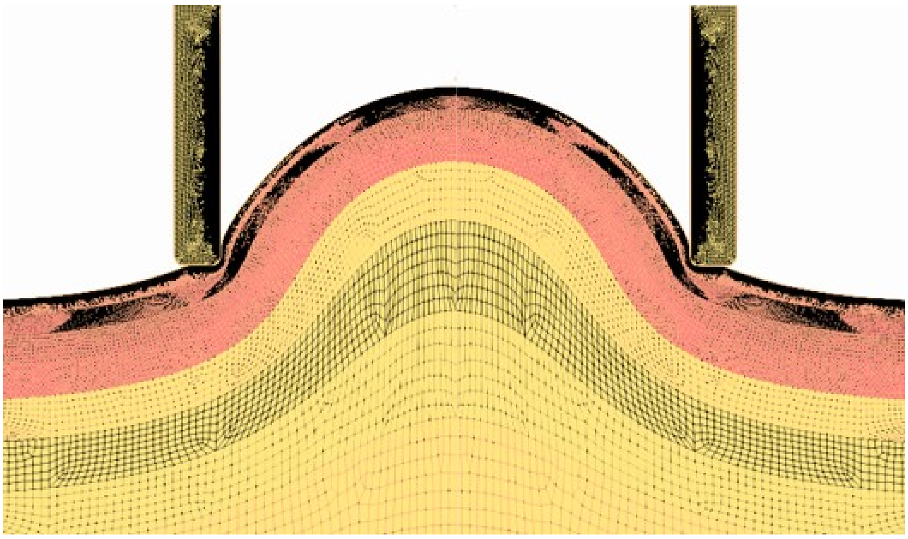

Figure 7: Axisymmetric finite element model of the suction experiment

3 Discussion/Conclusion

As a first result concerning this pilot study, it seems important to note that the measurements were carried out in a reasonable time scale (less than 20 min for each position) without any discomfort perceived by the participants. The estimations of the Young moduli for both layers (skin and fibroglandular tissues) gathered on Figure 8 provide a clustering of the data that makes us confident about the results obtained. The mean Young moduli (for all participants and all positions) estimated for the breast skin are 56.3 kPa ± 16.4 and 3.04 kPa ±1.17 for the fibroglandular tissue. Such values are coherent with the literature, with for example 58.4kPa proposed for skin by Hendriks et al. (2006) and 2.6 kPa (Sinkus et al., 2005) or 3.6 kPa (Xydeas

Volunteer	1	2	3	4	5	6	7
Upper Layer (skin)							
Position 1	62.2	55.9	72.3	49.0	40.5	57.4	48.3
Position 2	106	87.9	120	64.2	55.1	70.3	109
Position 3	69.9	62.0	78.1	64.1	75.1	51.1	40.2
Lower Layer (fibroglandular tissue)							
Position 1	3.19	2.57	3.52	4.39	3.02	5.41	3.45
Position 2	5.00	4.54	6.24	4.19	3.33	4.69	1.23
Position 3	4.42	3.70	4.91	2.81	2.33	3.16	0.45

Table 2: Young moduli [kPa] of the upper (skin) and lower (fibroglandular tissue) layers estimated for the seven volunteers

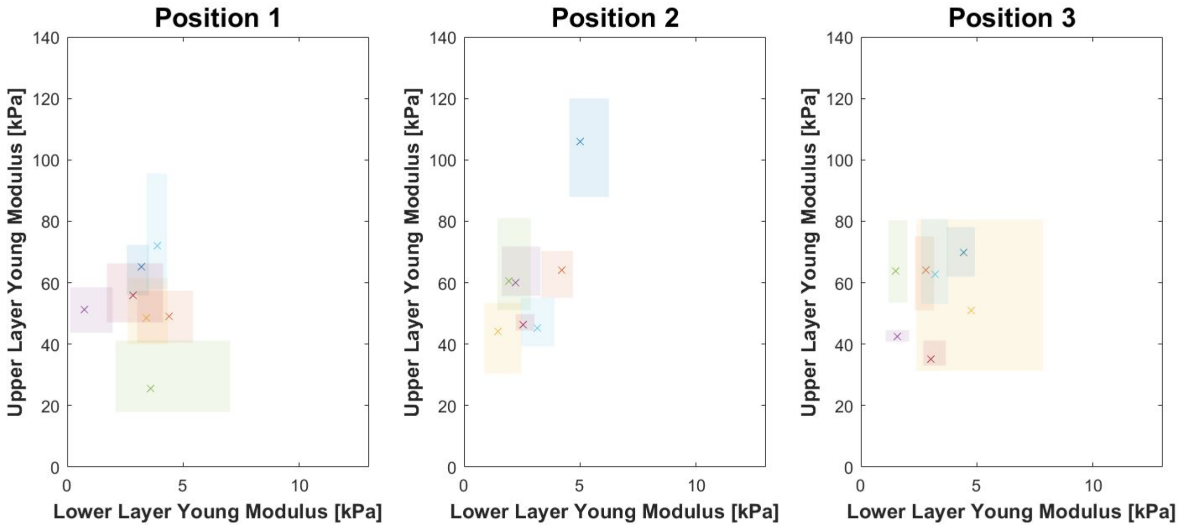

Figure 8: Young moduli and their uncertainty zones estimated for the seven volunteers, for each of the three positions. x: Young modulus ; Rectangular regions: uncertainty zones

et al., 2005) proposed for the fibroglandular tissue. Another interesting result concerns the moduli estimated for the three positions. It seems that the fibroglandular tissue stiffness estimated for the medium position 2 is in most cases higher than stiffness estimated for positions 1 and 3. This result has to be studied further in order to see whether any anatomical/morphological explanation could be given to explain such a difference.

Looking into the details of the results, it appears that the non-linearity of the pressure/volume curves (Figure 5) is more pronounced for smaller cups. This means that the linear regression with the estimation of the apparent stiffness is probably closer to the data for large diameter cups (with an overestimation of the apparent stiffness for smaller cups). It moreover strengthens the fact that the VLASTIC device should be used for small strains only with the estimation of the corresponding Young modulus. In addition to differences between the volunteers (age, weight, etc.) and measurement errors (leaks, poor positioning, etc.) that can explain the dispersion among results, one piece of data stands out (Figure 8, right-hand graph) with an uncertainty zone that is much larger than the other ones. This is probably due to the fact that for this particular volunteer, it was difficult to seal the cups, which may result in a less repeatable initial pressure than for the other volunteers. Finally, we should acknowledge that a number of parameters can have a significant influence on the results, such as temperature, the presence of gel inside the cups or the movements of the volunteer during the measurements. The corresponding artefact can, however, be avoided by taking a few precautions during the experiment.

In conclusion, it appears that the VLASTIC device allows for relatively fast and non-invasive in vivo measurements of skin and fibroglandular breast stiffness. The preliminary results provided in this paper are encouraging but should be confirmed in a clinical study that will include a much larger number of volunteers and patients.

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Declaration

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Babarenda Gamage, T. P., Malcolm, D. T., Maso Talou, G., Mîra, A., Doyle, A., Nielsen, P. M., and Nash, M. P. (2019). An automated computational biomechanics workflow for improving breast cancer diagnosis and treatment. *Interface Focus*, 9(4):20190034.

Bohte, A., Nelissen, J., Runge, J., Holub, O., Lambert, S., de Graaf, L., Kolkman, S., Van Der Meij, S., Stoker, J., Strijkers, G., et al. (2018). Breast magnetic resonance elastography: a review of clinical work and future perspectives. *NMR in Biomedicine*, 31(10):e3932.

Chung, J.-H., Rajagopal, V., Nielsen, P. M., and Nash, M. P. (2008). Modelling mammographic compression of the breast. In *International conference on medical image computing and computer-assisted intervention*, pages 758–765. Springer.

Connesson, N., Briot, N., Rohan, P., Barraud, P., Elahi, S., and Payan, Y. (2022). Bi-layer stiffness identification of soft tissues by aspiration.

Eder, M., Raith, S., Jalali, J., Volf, A., Settles, M., Machens, H.-G., and Kovacs, L. (2014). Comparison of different material models to simulate 3-d breast deformations using finite element analysis. *Annals of biomedical engineering*, 42(4):843–857.

Elahi, S. A., Connesson, N., Chagnon, G., and Payan, Y. (2019). In-vivo soft tissues mechanical characterization: volume-based aspiration method validated on silicones. *Experimental Mechanics*, 59(2):251–261.

Elahi, S. A., Connesson, N., and Payan, Y. (2018). Disposable system for in-vivo mechanical characterization of soft tissues based on volume measurement. *Journal of Mechanics in Medicine and Biology*, 18(04):1850037.

Gefen, A. and Dilmoney, B. (2007). Mechanics of the normal woman's breast. *Technology and Health Care*, 15(4):259–271.

Gefen, A. and Margulies, S. S. (2004). Are in vivo and in situ brain tissues mechanically similar? *Journal of biomechanics*, 37(9):1339–1352.

Girard, E., Chagnon, G., Gremen, E., Calvez, M., Masri, C., Boutonnat, J., Trilling, B., and Nottelet, B. (2019). Biomechanical behaviour of human bile duct wall and impact of cadaveric preservation processes. *Journal of the mechanical behavior of biomedical materials*, 98:291–300.

Han, L., Hipwell, J. H., Eiben, B., Barratt, D., Modat, M., Ourselin, S., and Hawkes, D. J. (2013). A nonlinear biomechanical model based registration method for aligning prone and supine mr breast images. *IEEE transactions on medical imaging*, 33(3):682–694.

Hendriks, F., Brokken, D., Oomens, C., Bader, D., and Baaijens, F. (2006). The relative contributions of different skin layers to the mechanical behavior of human skin in vivo using suction experiments. *Medical engineering & physics*, 28(3):259–266.

Kappert, K., Connesson, N., Elahi, S., Boonstra, S., Balm, A., van der Heijden, F., and Payan, Y. (2021). In-vivo tongue stiffness measured by aspiration: Resting vs general anesthesia. *Journal of biomechanics*, 114:110147.

Kerdok, A. E., Ottensmeyer, M. P., and Howe, R. D. (2006). Effects of perfusion on the viscoelastic characteristics of liver. *Journal of Biomechanics*, 39(12):2221–2231.

Lorenzen, J., Sinkus, R., Biesterfeldt, M., and Adam, G. (2003). Menstrual-cycle dependence of breast parenchyma elasticity: estimation with magnetic resonance elastography of breast tissue during the menstrual cycle. *Investigative radiology*, 38(4):236–240.

O'Hagan, J. J. and Samani, A. (2009). Measurement of the hyperelastic properties of 44 pathological ex vivo breast tissue samples. *Physics in Medicine & Biology*, 54(8):2557.

Ottensmeyer, M. P. (2002). In vivo measurement of solid organ visco-elastic properties. *Studies in health technology and informatics*, pages 328–333.

Rajagopal, V., Lee, A., Chung, J.-H., Warren, R., Highnam, R. P., Nash, M. P., and Nielsen, P. M. (2008). Creating individual-specific biomechanical models of the breast for medical image analysis. *Academic radiology*, 15(11):1425–1436.

Richey, W. L., Heiselman, J. S., Luo, M., Meszoely, I. M., and Miga, M. I. (2021). Impact of deformation on a supine-positioned image-guided breast surgery approach. *International Journal of Computer Assisted Radiology and Surgery*, 16(11):2055–2066.

Sinkus, R., Tanter, M., Xydeas, T., Catheline, S., Bercoff, J., and Fink, M. (2005). Viscoelastic shear properties of in vivo breast lesions measured by mr elastography. *Magnetic resonance imaging*, 23(2):159–165.

Tagliabue, E., Dall'Alba, D., Magnabosco, E., Tenga, C., Peterlik, I., and Fiorini, P. (2019). Position-based modeling of lesion displacement in ultrasound-guided breast biopsy. *International journal of computer assisted radiology and surgery*, 14(8):1329–1339.

Treloar, L. (1943). The elasticity of a network of long-chain molecules—ii. *Transactions of the Faraday Society*, 39:241–246.

Vavourakis, V., Eiben, B., Hipwell, J. H., Williams, N. R., Keshtgar, M., and Hawkes, D. J. (2016). Multiscale mechano-biological finite element modelling of oncoplastic breast surgery—numerical study towards surgical planning and cosmetic outcome prediction. *PloS one*, 11(7):e0159766.

Weis, J. A., Miga, M. I., and Yankeelov, T. E. (2017). Three-dimensional image-based mechanical modeling for predicting the response of breast cancer to neoadjuvant therapy. *Computer methods in applied mechanics and engineering*, 314:494–512.

Xydeas, T., Siegmann, K., Sinkus, R., Krainick-Strobel, U., Miller, S., and Claussen, C. D. (2005). Magnetic resonance elastography of the breast: correlation of signal intensity data with viscoelastic properties. *Investigative radiology*, 40(7):412–420.