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Evaluation and comparison of the nonlinear elastic properties of the soft tissues of the breast

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***Abstract*— As the number of breast cancer patients increases, there is an increasing need for accurate non-invasive methods for the diagnosis of breast cancer. It is possible that the nonlinear elastic properties of soft tissues of the breast can be used as a basis for diagnostic methods. Therefore, we have proposed a robotic palpation system for diagnosis based on the nonlinear elastic properties of tissue. Here, we measured the nonlinear elastic properties of soft tissues of the breast using creep tests and three parameters of the nonlinear elastic model were acquired. Two of these parameters are significantly different among soft tissues of the breast and that the magnitude of these parameters was determined by the tissue structure. These parameters could be used to differentiate between tissue types and aid in the diagnosis of breast cancer.**

I. Introduction

In recent years, early detection of breast cancer has been possible because of advances in imaging technology. However, it is difficult to make a definite diagnosis by palpation or imaging modalities, and invasive examinations are needed to determine whether a breast tumor is benign or malignant. Therefore, accurate non-invasive diagnostic methods are needed to alleviate the patient's mental burden.

Researchers have focused in recent years on the stiffness of a malignant tumor which is measured qualitatively on palpation, because the following three stiffness properties of physiological tissue have been reported [1], [2]. First, physiological tissue exhibits nonlinear elasticity. Second, the elasticity of malignant tumors is greater than that of benign tumors and of normal tissue. Third, the rate of increase in elasticity of malignant tumors is greater than that of benign tumors and normal tissue. These characteristics suggest that the nonlinear elastic properties of soft tissues could have diagnostic potential. Therefore, many studies have reported techniques to measure tissue elasticity, including elastography imaging. The aim of elastography is to induce motion within the target tissue by an external force and conventional medical imaging modalities are used to measure tissue deformation, from which the mechanical properties can be reconstructed.

There are limitations in the present elastography protocols. Elastography research is typically dedicated to imaging contrast in linear stiffness under the assumption of very small deformation. Some researches have reported nonlinear elastography imaging [3], [4]. The evaluation of nonlinear stiffness of tissues is the need for sufficiently large deformation to detect a deviation from linear response. However, it is actually very difficult to measure large deformations using elastography. Furthermore, elastography does not use the force information to reconstruct the mechanical properties because it is applied as an adjunct to existing imaging modalities. However, tissue elasticity measured by elastography is relative to that within the field of measurement. Therefore, it is possible that the elasticity of tumors relative to that of normal tissue may result in misdiagnosis. In addition, the elasticity of normal breast tissue changes periodically. To establish a diagnostic approach based on the nonlinear elasticity of tumor tissue, a method to measure large deformation of tumor tissue and absolute nonlinear elasticity is needed.

To fulfill this objective, we have proposed a robotic palpation system to evaluate the nonlinear elasticity properties of tissues. Figure 1 shows our system concept. The proposed robotic system is a system that strains the breast tissue, akin to palpation, measures the mechanical reaction of the breast, and identifies the parameters of a nonlinear elastic model. A limitation of this approach is that it is difficult to differentiate the deformation of tumor tissue from that of the entire breast because the breast is composed of several kinds

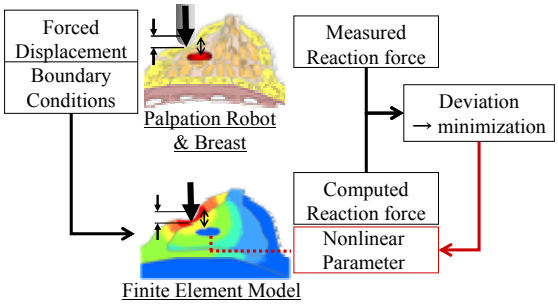

Fig. 1. Scheme of our robotic palpation system.

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of tissues with different mechanical properties. We investigate the nonlinear reaction of the breast by finite element simulation, and consider the conditions of robot, such as section area of indenter, to differentiate the deformation of tumor tissue. It is necessary to measure the mechanical properties of each tissue type, particularly the nonlinear stress–strain relationship and understand the elasticity of each tissue, including the degree of nonlinearity for simulation.

Some studies have reported about measurements of the nonlinear elastic properties of breast tissues. The nonlinear elastic properties of breast tissues were first reported by Krouskop et al. [1].They measured the elasticity of breast tissues under 5% and 20% compression. Subsequently, Wellman [2] and Samani et al. [5] measured breast tissue stiffness using uniaxial compression tests. Krouskop et al. [1] and Wellman et al. [2] were reported that the elastic properties were independent of strain rate from comparison of several strain rates.

However, there are limitations in the present studies of measurements of the nonlinear elastic properties. breast tissues have viscoelastic properties because these tissues contain high collagens that have viscous properties. To date, the nonlinear viscoelastic properties of breast tissue have not yet been reported in any detail. Although the shear properties of breast tissue have not yet been reported, some reports [6] have revealed that doctors can feel the shear elasticity of tissues by palpation. While isotropic materials show a direct relationship between shear and longitudinal elasticity, anisotropic materials do not show such relationships. For this reason, physiological tissues are anisotropic, meaning the measurement of shear elasticity is necessary. We have already reported a nonlinear elastic model constructed using the torsional creep test [7], [8] and the reliability of this model has been verified by comparing deformation within hog liver and a simulation.

The objective of the present study is to measure the nonlinear elastic properties of soft tissues in the breast and to compare the results among these tissues. In this paper, we performed shear and viscoelastic tests using breast soft tissues.

II. Methods

The torsional creep test was used to measure the nonlinear elastic properties of breast tissues (fat, fibroglandular and muscle tissue) and compared the results using the nonlinear elastic model. Using the obtained results, we compared the parameter between each tissue type, and whether the magnitude of each parameter is associated with tissue type. The creep tests showed that the stiffness–strain relationship was approximated by the nonlinear elastic model. The three parameters of the nonlinear elastic model were measured in each tissue.

A. Nonlinear elastic model

We have already reported a nonlinear elastic model of hog liver in which the model was constructed by the torsional creep test [7], [8]. The creep test is often used to measure the viscoelastic properties of materials by measuring the step response. In our previous work, the steady state of the step response, after a sufficient time interval, exhibits the low-frequency characteristics described in (1).

$$G\frac{d^k\gamma}{dt^k}=\tau \tag{1}$$

where G is the viscoelasticity, t is time, γ is the shear strain, k is the order of derivative and τ is the shear stress.

Equation (2) is obtained if (1) is solved by the creep test.

$$\gamma=\frac{\tau_c}{G\,\Gamma(1+k)}t^k=\gamma_c t^k \tag{2}$$

where τ_c is constant shear stress, γ_c is the coefficient deciding the strain value and $\Gamma()$ is the gamma function.

A creep test for each stress in the step response was carried out while the viscoelasticity G and strain γ_c for each stress were calculated using (2). Our previous work using a hog liver showed that the nonlinear properties can be modeled using the quadric function of strain described in (3) and (4).

$$G(\gamma)=\begin{cases} G_o & (\gamma<\gamma_0) \\ G_0(1+a_\gamma(\gamma-\gamma_0)^2) & (\gamma>\gamma_0)\end{cases} \tag{3}$$

$$\tau=\begin{cases} G_o\gamma & (\gamma<\gamma_0) \\ G_0(1+a(\gamma-\gamma_0)^2)\gamma & (\gamma>\gamma_0)\end{cases} \tag{4}$$

where G is the viscoelasticity, G_o is the viscoelastic modulus of the linear part, a_γ is the coefficient deciding the change of G, γ is the shear strain and γ_0 is the point at which nonlinearity is observed. Figure 2 shows a typical graph of viscoelasticity G vs. strain γ determined using (3), and Figure 3 shows a typical graph of stress τ vs. strain γ determined using (4).

B. Test condition

We used a rheometer (AR-G2, TA Instruments) to measure the torque loaded on the sample and the torsional angle of the

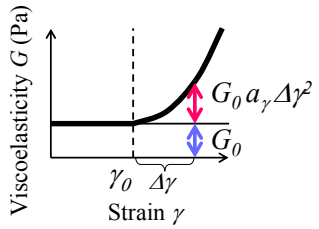


Fig. 2. Relationship between viscoelasticity G and strain γ. This Fig. is shown to explain (3).

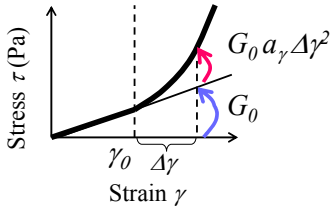
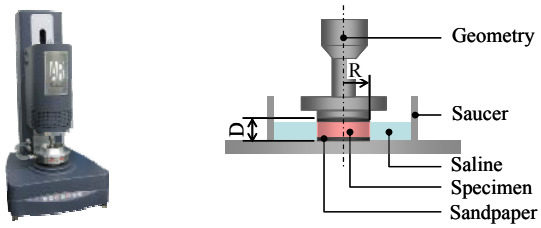


Fig. 3. Relationship between τ and strain γ. This Fig. is shown to explain (4).



(a) The AR-G2 rheometer (b) Test condition

Fig. 4. The rheometer and specimen placement

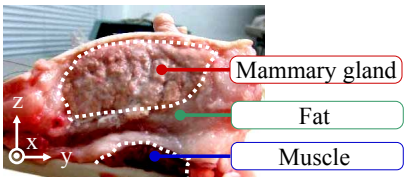


Fig. 5. A representative cross-section of a hog breast.

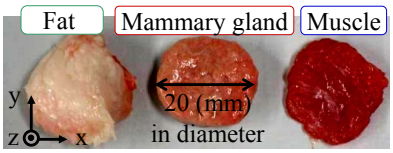


Fig. 6. Representative test specimens.

sample (Fig. 4). The shear modulus of the sample was then calculated based on these results. We used hog breast in the present study because it is mechanically similar to human breast. We measured the material properties of fat,fibroglandular and muscle tissue, the three main tissue types within the breast. Figure 5 shows a typical hog breast cross section. Each soft tissue type was cut into a circular, cylindrical shape (20 mm in diameter, height ~5 mm; Fig. 6) and placed on a measurement table. The specimens were not frozen at any time during the study. For each test, the test samples were soaked in normal saline solution at a temperature of 35°C and sandpaper was attached to the top plate and the measurement table to prevent sliding. The mean stress and strain values for each tissue are presented below.

C. *Methods*

The creep tests were performed on samples prepared as described above. The load share stress ranged from 100 to 1000 Pa and strain data were recorded for 60 s at each stress. Each test was performed at intervals of 180 s. Measurements were performed in ascending order of load because the samples experience fatigue as the test is conducted.

III. Results

A. *Results of creep tests*

Creep tests were performed on 12 fat, 19 fibroglandular, and 6 muscle tissue samples taken from 6 hog breasts. Typical results under a load stress of 100 Pa for one fat sample are shown in Fig. 7 and are represented by a strain–time graph. Data obtained from 8 s onwards correspond to the steady state approximated by (2). The coefficient of determination (R^2) exceeded 99% for each experiment. From these results, we confirmed that the viscoelastic model based on (2) may be applicable to soft tissues of the breast. Therefore, we calculated the nonlinear parameters in (3).

B. *Determining the nonlinear parameters*

The viscoelasticity G and strain γ_c for each stress were calculated using (2). Then, the viscoelasticity–strain relationship was approximated by (3) for each sample as follows. There are N experimental data in total. On the assumption that the n^{th} and the subsequent data are approximated by a quadratic function, the parameters of (3) are calculated using the method of least squares. The n ranges from 1 to $N–3$. Then, the determination coefficient R^2 is calculated for each set of three parameters. Finally, the set of parameters showing the greatest R^2 of N–3 sets was chosen as the optimal set. Based on these calculations, the maximum coefficient of determination R^2 exceeded 85% for each sample. These results indicate that the nonlinear properties of breast tissues and those of the model are similar. Therefore, the model developed using (3) can reproduce the nonlinear responses of soft tissues of the breast. As an example, the nonlinear properties of fibroglandular tissue and the response of our model are shown in Fig. 8. The mean, standard deviation (SD) and standard error (SE) were calculated for each parameter in each tissue type, and the data are shown in Table 1.

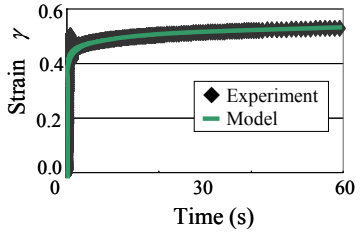


Fig. 7. Comparison of measurement data and model data for fat at 100 Pa. The black line shows the experimental results and the green line shows the response of our model.

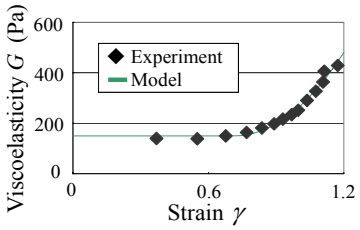


Fig. 8. Stiffness–strain relationship of mammary gland tissue. The black line shows the experimental results and the green line shows the response of our model. Note the close correlation between experimental data and model.

TABLE I
NONLINEAR ELASTICITY PARAMETERS IN THREE TISSUE TYPES

Tissue type	n	Parameter	Mean	SD	SE
Fat	12	G_0 Pa	9.9×10	5.1×10	1.5×10
		γ_0	0.87	0.37	0.11
		a_γ	2.1	1.5	0.43
Mammary gland	19	G_0 Pa	1.6×10^2	5.8×10	1.3×10
		γ_0	0.44	0.20	0.045
		a_γ	21	13	2.9
Muscle	6	G_0 Pa	3.4×10^2	1.3×10^2	5.2×10
		γ_0	0.51	0.11	0.043
		a_γ	6.2	1.3	0.55

IV. Discussion

In this chapter, we compare the experimental results among the three tissue types. We discuss whether there is the characteristic value for each parameter in each tissue type and whether there is a relationship between the magnitude of the parameter and the tissue type.

A. Characteristic values of each parameter

If the parameters have characteristic values, we can identify the tissue by parameter identification. If significant differences in the nonlinear parameters are found between each tissue type, the nonlinear parameters are specific for each tissue type and can be used to differentiate between the tissues. The statistical test analysis of variance is usually used to compare means among three or more groups. In this paper, we instead compared the means by determining whether the 95% confidence intervals (CI) for the means overlapped. The 95% CI for a mean is a range of values in which the population mean is estimated with 95% probability. If the 95% CIs for two means do not overlap, the means are significantly different at a 5% level [9]. If the values for a population are normally distributed, the CI is determined using (5).

$$X - t \cdot SE < \mu < X + t \cdot SE \tag{5}$$

where X is the sample mean, t is the SD from the mean required to contain 95% of the area of the t distribution determined by sample size. Figure 9 shows the 95% CIs for each parameter in each tissue type.

As shown in Fig. 9, the 95% CI of the viscoelastic modulus of the linear part G_o did not overlap among the three tissues. A similar result was obtained for the coefficient for the change in stiffness a_γ. However, the 95% CIs of the strain did overlap and the characteristics of soft tissue changed, showing nonlinearity γ_0 between fibroglandular and muscle tissue. Thus, there were significant differences in the parameters G_o and a_γ, indicating that these parameters had characteristic values for each tissue type and the type of tissue could be differentiated by parameter identification.

B. Relationship between the magnitude of each parameter and tissue type

We next focused on the magnitude of parameters G_o and a_γ for each tissue type. G_o and a_γ of fat tissue were approximately 100 and 2, respectively. Fat tissue is a loose connective tissue that is soft and shows nearly linear elasticity. In contrast, fibroglandular tissue shows marked nonlinear elasticity because it contains abundant collagen, a sticky substance. For this reason, although the G_o of fibroglandular tissue was about 1.3 times that of fat tissue, the a_γ of fibroglandular tissue was about 10 times that of fat tissue. Finally, muscle tissue is a tough material that generates movement. Therefore, the corresponding G_o and a_γ values of muscle tissue were about 3.4 and 3 times those of fat tissue. These results suggest that the magnitude of each parameter is related to tissue structure.

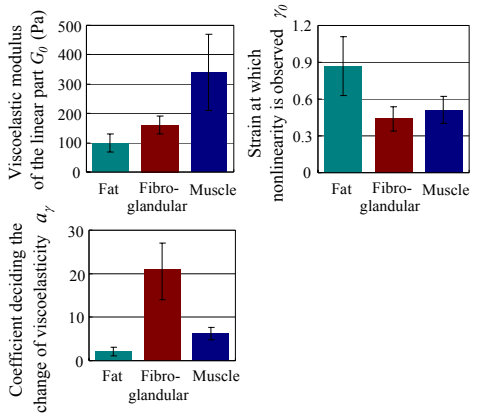


Fig. 9. The 95% confidence interval for each parameter in each tissue type.

V. Summary And Future Work

In this study, we measured the nonlinear elastic properties of the soft tissues which compose the breast, including fat, fibroglandular and muscle tissue, using the creep test. Based on the experimental results, we confirmed that the nonlinear parameters G_o and a_γ had characteristic values for each tissue type, and the tissue types could be distinguished by parameter identification. These results suggested that the magnitude of each parameter is determined by the tissue structure.

In future work, we will examine the effect of deformation of the breast on the distribution of these parameters. We will perform deformation analysis using the finite element method, and compare the results with *in vivo* experimental results. Using the results, we will explore the potential for parameter identification, and hence develop a robotic palpation system.

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