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Linear and Nonlinear Elastic Modulus Imaging: An Application to Breast Cancer Diagnosis

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Abstract

We reconstruct the *in vivo* spatial distribution of linear and nonlinear elastic parameters in ten patients with benign (five) and malignant (five) tumors. The mechanical behavior of breast tissue is represented by a modified Veronda–Westmann model with one linear and one nonlinear elastic parameter. The spatial distribution of these elastic parameters is determined by solving an inverse problem within the region of interest (ROI). This inverse problem solution requires the knowledge of the displacement fields at small and large strains. The displacement fields are measured using a free-hand ultrasound strain imaging technique wherein, a linear array ultrasound transducer is positioned on the breast and radio frequency echo signals are recorded within the ROI while the tissue is slowly deformed with the transducer. Incremental displacement fields are determined from successive radio-frequency frames by employing cross-correlation techniques. The rectangular regions of interest were subjectively selected to obtain low noise displacement estimates and therefore were variables that ranged from 346 to 849.6 mm². It is observed that malignant tumors stiffen at a faster rate than benign tumors and based on this criterion nine out of ten tumors were correctly classified as being either benign or malignant.

Index Terms

Breast tumor; inverse problem; linear and nonlinear elasticity imaging; ultrasound imaging

I. Introduction

ACCORDING to the National Institutes of Health, on an annual basis about 200 000 women in the USA are diagnosed with breast cancer and more than 40 000 die from this disease. Early detection is crucial for good prognosis and the risk of breast cancer increases with a woman's age. Therefore, the current recommendation is for all women to undergo yearly mammography screening beginning at age 40 [1]. Even though mammography is widely used in clinical practice to detect cancers, its limitations are well recognized. In particular, there is a significant problem in screening women with dense breasts, especially those women at higher risk for breast cancer. Magnetic resonance imaging (MRI) and ultrasound have been suggested as alternative methods for screening women at high risk for breast cancer who are not good candidates for mammography. These modalities, especially ultrasound, are commonly used for adjunctive imaging following indeterminate mammography results. Even with these adjunctive imaging procedures, the definitive diagnosis is based on biopsy. Currently biopsy yields a benign result in more than 75% of patients and it is the most costly component of the breast cancer screening program [2]. There is a clear need for diagnosing benign lesions to be able to reduce the number of benign breast biopsies.

In the last two decades elasticity imaging, also known as elastography, has demonstrated potential for diagnosing breast cancer. In elasticity imaging, mechanical properties of tissues are imaged and correlated with pathology. In elasticity imaging, displacement or velocity fields are measured using ultrasound imaging [3]–[5], magnetic resonance imaging (MRI) [6]–[9], or computed tomography (CT) [10] and are used to infer the elastic and/or viscoelastic properties of tissues. When using ultrasound imaging (as is the case in this paper) it is assumed that, for relatively small deformations, the random speckle pattern follows tissue motion. Therefore, the backscattered echo signals or radio frequency data recorded at successive increments of deformation can be used to determine the displacement field *in vivo* with cross-correlation or other image registration techniques. Differentiating this displacement field in space leads to a strain image.

Strain imaging [3] is among the most common, if not the most common, form of ultrasound elastography. A strain image depicts the local deformation of tissue in response to a gentle compression. In breast cancer applications, axial strain imaging has been shown to significantly improve both sensitivity and specificity over ultrasound alone [11]–[20].

It has been long recognized that strain contrast, an approximation of the relative stiffness between a lesion and its background depends upon the total applied deformation of the tissue [21]–[24], [13], [25]. The observed variation of strain contrast with overall applied strain is recognized to arise from the nonlinear stress-strain behavior exhibited by breast tissues, as measured and reported in [26]–[29]. That is, the slope of the stress-strain curve is (usually) quite different at low strain than at high strain. Measurements of a large number of breast tissue samples *ex vivo* lead the authors of [29] to conclude that the nonlinear characteristics of the stress-strain curve of breast tissues might be exploited to aid in the differentiation of breast masses.

Several teams have been motivated by these and earlier observations to attempt to image the nonlinear response of tissues. Nitta and Shiina [30], for instance, attempted to quantify this

effect with what could be called “strain-slope” images. These are constructed by assuming strain contrast is a linear function of overall applied strain. Their model fails to account for geometric nonlinearity in the deformation, and models the tissue response as uniaxial. Skovoroda *et al.* [21], [24], [25] also focused largely on studying changes in strain contrast with overall applied strain. Their treatment of quantitative reconstruction [21] accounts for large deformation, but assumes a linear (neoHookean) stress-strain law. More recent efforts account for both geometric and material nonlinearity [31]–[33], and aim to reconstruct quantitatively both the linear elastic stiffness (i.e., shear modulus μ or Young’s modulus $E = 3\mu$ for an incompressible material), and a nonlinearity parameter of the tissue response. These studies have all focused on either simulated data or phantom data. Our group, however, has recently demonstrated the feasibility of measuring both the linear elastic modulus distribution and the tissue nonlinearity *in vivo* [34].

The purpose of the present study is to provide an initial indication of the potential for differentiating benign and malignant breast masses *in vivo* based on nonlinear parameter reconstructions from *in vivo* data. For that purpose, we took advantage of the availability of previously collected ultrasound elastography data, and applied the modulus reconstruction methods described in [34]. The archived ultrasound data is 2-D, and hence a 2-D (plane stress) approximation of the deformation is used to reconstruct the properties, as discussed herein. The data selected correspond to five patients with the most common solid benign breast lesions (fibroadenomas) and five patients with the most common malignant breast lesions (invasive ductal carcinomas). We reconstruct both linear elastic modulus and tissue mechanical nonlinearity distributions for all patients. Our findings suggest that linear elastic modulus contrast is independent of lesion type, while nonlinear response is significantly higher in invasive ductal carcinomas than in fibroadenomas.

II. Methods

A. Data Acquisition

In the data investigated, approval for the human subject study was obtained from the appropriate Institutional Review Boards and the study was also compliant with the U.S. Health Insurance Portability and Accountability Act.¹ The patient pool from which subjects were chosen, and the distribution of disease types are described in detail in [18]. The pathology of each tumor was determined by either percutaneous (core) or excisional biopsy.

In vivo breast scanning was performed by clinicians using Siemens SONOLINE Elegra ultrasound scanners equipped with high-frequency linear array transducers (either VFX13 or 7.5L40, Siemens Healthcare USA Inc., Mountain View, CA). A real-time strain imaging algorithm [35] was implemented on the Elegra and used during echo data acquisition to provide visual feedback of strain image quality to ensure the quality of radiofrequency echo data being recorded. The detailed protocol for data acquisition under the guidance of a real-time strain imaging system can be found elsewhere [13]. The data used in this study were selected from a large database of over 450 cases. From this database, we selected five fibroadenomas and five invasive ductal carcinomas. Criteria for inclusion were 1) that the compression was initiated with minimal preloading, 2) the total applied strain was at least 12%, and 3) the “displacement quality metric” [36] remained above 0.8 over a strain range of at least 10%.

To track large accumulative deformations (approximately 12%) required for nonlinear elasticity imaging, we first track motion sequentially through multiple frames (from the first

¹Available online: <http://www.cms.gov/hipaageninfo/>

ultrasound frame to the N th frame) similar to the multi-compression technique [37] selecting frame pairing to achieve approximately 1.0% frame-average strain. Our early work [38] has demonstrated that, with the addition of a motion continuity constraint, larger tissue deformation can be tracked from frame-to-frame using a modified block-matching algorithm. A frame-to-frame strain of 1.0%–1.5% was an empirical selection to balance signal cross correlation and displacement estimate accuracy [36]. Next we map all displacement estimates in the sequence to the coordinate system of the first echo frame by using B-spline interpolations. More specifically, offline motion tracking was performed between two adjacent radio-frequency (RF) echo frames (from the i th frame to the $(i + 1)$ th frame) using a modified block-matching algorithm [38]. Modifications to the classical block-matching algorithm are to constrain motion continuity using a dynamic programming technique so that the occurrence of large motion tracking errors is minimized. During motion estimation between two echo frames, displacement estimates from the modified block-matching with a small (approximately 0.5 mm [height] by 1 mm [width]) tracking kernel are first made on a $0.2 \text{ mm} \times 0.2 \text{ mm}$ sample grid with RF-sample precision. Then, sub-sample displacement estimates (necessary for modulus inversion) are obtained with quadratic interpolation of the initial block-matching results.

B. Formulation of the Nonlinear Inverse Elasticity Problem

In this section, we present the nonlinear constitutive relation used to model breast tissue and briefly review the iterative solution strategy for solving the inverse elasticity problem. For a detailed discussion and derivation of the underlying algorithms the reader is referred to [31].

We pose the inverse elasticity problem as a constrained minimization problem as follows.

Given n measured displacement fields $\mathbf{u}_{\text{meas}}^1, \dots, \mathbf{u}_{\text{meas}}^n$, find the material properties $\beta = [\beta_1, \beta_2] = [\mu, \gamma]$ such that the objective function

$$\pi = \frac{1}{2} \sum_{i=1}^n w_i \|\mathbf{T} \mathbf{u}^i - \mathbf{T} \mathbf{u}_{\text{meas}}^i\|_0^2 + \frac{1}{2} \sum_{j=1}^2 \alpha_j R(\beta_j) \quad (1)$$

is minimized under the constraint that the predicted displacement fields satisfy the equations of equilibrium and boundary conditions given in (3)–(5). In other words, we seek that distribution of material parameters $[\mu, \gamma]$ which leads to the predicted displacement fields $\mathbf{u}^i$ that attain the global minimum in (1).

In the objective function (1) the first term is the displacement matching term which measures the discrepancy between the measured and predicted displacement fields in the L_2 norm denoted by $\|\cdot\|_0$. The summation indicates that several measured displacement fields may be matched simultaneously. Thus, we need to scale each term with a weighting factor w_i to ensure that small and large displacements contribute equally to the objective function. The tensor $\mathbf{T}$ is a diagonal tensor that allows a different weight for each displacement component. This is important because estimates of the lateral displacement component (perpendicular to the transducer axis) are low precision relative to the axial displacement component (parallel to the transducer axis). Therefore, it would be prudent to attach a smaller weight to the lateral displacement component or discard its contribution to the objective function completely. In this work, we completely discard the low precision lateral displacement components from the minimization process. Previous elastic property reconstructions on tissue mimicking phantoms and synthetic data have demonstrated that accurate modulus reconstructions can be obtained in this manner [39], [40].

The second term in (1) is the regularization term and ameliorates the ill-posed nature of the inverse problem. The regularization parameter α_j is noise dependent and can be determined

using the L-curve method or Morozov's principle [41]. We have chosen the total variation diminishing (TVD) regularization [42] which is implemented in the form

$$R(\beta_j) = \int_{\Omega_0} \sqrt{|\nabla \beta_j|^2 + c^2} d\Omega_0. \quad (2)$$

Here, c is chosen to be a small constant to ensure that the regularization contribution is smooth when $\nabla \beta_j = \mathbf{0}$. The regularization contribution may be thought of as a penalty term that controls the smoothness of the solution. TVD regularization has proven to work well for our purpose as it penalizes fluctuations in the parameters without regard to their steepness and thus preserves sharp inclusion boundaries.

The equations of equilibrium corresponding to the i th measurement are given by

$$\nabla \cdot (\mathbf{F}^i \mathbf{S}^i) = \mathbf{0} \text{ in } \Omega_0 \quad (3)$$

$$\mathbf{u}^i = \mathbf{g}^i \text{ on } \Gamma_g \quad (4)$$

$$\mathbf{F}^i \mathbf{S}^i \cdot \mathbf{n} = \mathbf{h}^i \text{ on } \Gamma_h. \quad (5)$$

Here, $\mathbf{F}^i$ is the deformation gradient and $\mathbf{S}^i$ is the second Piola–Kirchhoff stress tensor, which is derived from the strain energy density function (discussed in the following paragraph). Tractions are denoted by $\mathbf{h}^i$, prescribed displacements by $\mathbf{g}^i$, and $\mathbf{n}$ is the boundary outward unit normal vector. The boundaries for the prescribed displacements on Γ_g and for the traction on Γ_h are assumed to satisfy the following conditions: $\partial\Omega_0 = \overline{\Gamma_g \cup \Gamma_h}$, and $\Gamma_g \cap \Gamma_h = \emptyset$. We discuss the boundary conditions in more detail below.

We have used a modified version of the Veronda–Westmann strain energy density function for an incompressible material in three dimensions. It consists of one linear parameter and one nonlinear parameter as opposed to the original Veronda–Westmann model [43] with three hyperelastic parameters. The strain energy density is given by

$$W = \mu \left(\frac{e^{\gamma(I_1-3)} - 1}{\gamma} - \frac{I_2 - 3}{2} \right). \quad (6)$$

Here, I_1 and I_2 are, respectively, the first and second principal invariants of the Cauchy Green tensor, $\mathbf{C} = \mathbf{F}^T \mathbf{F}$. Further μ represents the shear modulus of the material at small strains and γ is a parameter that determines the exponential increase in stiffness with increasing strain. We refer to γ as the nonlinear parameter, or simply, the “nonlinearity.” Under plane stress conditions, the strain energy density function above yields the following expression for the second Piola–Kirchhoff stress tensor

$$S_{ij} = \mu \left[2e^{\gamma(I_1+1/I_2-3)} \left(\delta_{ij} - \frac{C_{ij}^{-1}}{I_2} \right) - \frac{\delta_{ij}}{I_2} - \left(I_2 - \frac{I_1}{I_2} \right) C_{ij}^{-1} \right] \quad (7)$$

where δ_{ij} is the Kronecker symbol.

In ultrasound based elasticity imaging, the displacement data is typically collected in a plane. As a result a simplifying approximation that reduces the 3-D problem to a 2-D one must be made. There are two classical 2-D models of elastic behavior: plane strain and plane stress. The plane strain approximation applies to objects that are confined in the out-of-plane

(i.e., elevation) direction. The plane stress approximation applies to objects that are unconstrained in the out-of-plane direction. As the breast is unconfined during compression, the plane stress approximation seems appropriate. Furthermore, the inverse problem based on the plane stress approximation is much better conditioned than the plane strain approximation [44], [45]. Hence, it may be expected that reconstructions from the plane stress approximation will be more accurate than those from the plane strain approximation. For this reason we use the plane stress approximation.

Below we briefly review the steps used to solve the inverse elasticity problem.

1. Solve the forward problem (3)–(5) for the predicted displacements.
2. Solve the adjoint problem which is driven by the mismatch in the predicted and measured displacements.
3. Evaluate the objective function and its gradient with respect to the material parameters μ and/or γ using the solution to the forward and adjoint problems.
4. Use the gradient and objective function values in limited-memory BFGS algorithm [46], which returns with an updated material parameter distribution.
5. Repeat steps 1–4 until convergence.

The principal computational cost of the algorithm above is associated with solving the forward nonlinear elasticity problems. This cost is significantly reduced by employing a continuation strategy in the material parameters. A detailed description of this strategy and other aspects of the inverse elasticity problem is given in [31] and [32]. This algorithm was implemented in a Fortran 90 code. Sections of the code that assemble the finite element matrix were multi-threaded in order to reduce time by making use of the multi-core architecture of the computer. Further speed is possible by using a parallel linear equation solver.

C. Solution of the Nonlinear Inverse Elasticity Problem

We apply our inversion strategy, discussed in Section II-B, to create images of the shear modulus and the nonlinear parameter of ten tumor lesions with five benign and five malignant tumors. Twelve displacement fields with overall strain levels varying from 1% to 12% were acquired from each patient as described in Section II-A. We solve the inverse problem sequentially in a two-step process as described in [32]. In the first step, we set the nonlinear parameter $\gamma = 2$, and minimize the objective function for the shear modulus using one displacement field at about 1% overall strain. In a second step we reconstruct the nonlinear parameter γ using the frame in the displacement field closest to about 12% overall applied strain, while fixing the shear modulus to the previously reconstructed distribution. In this way, the γ reconstructions are all performed at the same overall strain, in order to avoid any bias that might be introduced otherwise.

The grid spacing on which we determine the displacements of nine datasets is about $0.1497 \text{ mm} \times 0.1875 \text{ mm}$ (axial $\times$ lateral) and for the remaining dataset the grid spacing is $0.1497 \text{ mm} \times 0.1705 \text{ mm}$. The area of the rectangular domain varies from 346 mm^2 to 849.6 mm^2 . We downsample the displacement data by a factor of 4 in each direction and reconstruct the linear and nonlinear elastic properties on the same coarse mesh. This downsampling effectively smooths the displacement data and facilitates the computation. The final meshes have a total number of nodes ranging from 816 to 1935. Tables I and II list the relevant mesh parameters for the images of the fibroadenomas and the invasive ductal carcinomas, respectively. The optimization variables μ and γ , as well as the measured and predicted displacement fields, are all represented with the same standard bilinear finite element shape functions.

The constrained optimization problem converges in about three minutes on a quad-core 3-GHz computer. The lower bounds for the shear modulus and the nonlinear parameter are set to be 1 and the upper bounds are chosen to be sufficiently large in order to prevent the material reconstructions from attaining the upper bound. The lower bound for the shear modulus does not influence the final reconstruction, because it is recovered only up to a multiplicative factor. This is because we do not impose any nonzero traction boundary condition in our boundary value problem. The nonlinear parameter γ is reconstructed uniquely if its value is specified at some location in the domain, or if a lower bound is specified [47]. We adopt the latter approach and select the lower bound to be one. We chose the same regularization parameter for all tumor reconstructions, that is, we set the regularization parameter for γ to $\alpha_\gamma = 2.0 \times 10^{-4}$ and for μ to $\alpha_\mu = 5.0 \times 10^{-6}$. We do so assuming that the noise level for all data is of the same order and thus penalize them all equally. This assumption is reasonable, as we acquire the patient RF-data with the same type of ultrasound device and compute the displacements with the same algorithm for all tumors.

Our reconstruction algorithm requires specification of boundary conditions on the four sides of the reconstruction domain. We model the top edge of the image domain as perfectly lubricated, consistent with the use of a lubricating gel between the transducer and skin. We assume the tissue is free to expand laterally on the lateral edges, and along the bottom of the imaged region. The latter assumption is less justifiable than the former, and liable to give rise to artifacts near the bottom boundary. In addition, we specify the axial displacement to be equal to the measured axial displacement on all four boundaries of the image domain. These assumptions are all in accord with the methods described in [34]. It is known that errors in these assumptions can lead to artifacts in the reconstructed properties. In the case of plane stress reconstructions, those errors tend to stay confined near the boundaries [48].

Finally, we have investigated solution dependence on variations in the initial guess, and observed that the recovered linear and nonlinear material parameter reconstructions were independent of this guess. This behavior is consistent with the uniqueness of the inversion, which may be expected from the results of [47].

D. Analysis of Shear Modulus and Mechanical Nonlinearity Images

The tumor boundaries are identified by hand on the shear modulus image. In some circumstances, guidance from the corresponding B-mode image was used to resolve ambiguity of boundary location. Average values of the lesion stiffness (shear modulus μ) and mechanical nonlinearity (γ) were obtained by computing the mean of twenty evenly spaced pixels well within the tumor boundaries. Since the stiffness changes from high to low values on the interface, the reconstructed value of stiffness near an interface tends to be lower than in the interior. Furthermore, the precise location of the tumor interface may be expected to be different in one modality than in another. By selecting our twenty sampling points unequivocally within and far from the tumor boundaries, we attempt to minimize the impact of these effects.

III. Results

The reconstructions for the shear modulus and the nonlinear parameter are presented in Figs. 1–10 together with a B-mode ultrasound image and an axial strain image at small strain for each tumor. The greyscale for the nonlinear parameter γ images was chosen to be the same across all tumors in order to facilitate a direct comparison between them. The greyscale for the shear modulus μ images have all been selected to subjectively maximize inclusion visibility. The tumor boundaries are indicated by yellow curves in the shear modulus μ and nonlinear parameter γ images. We note that the shear modulus image is used to determine the tumor boundary, and that same boundary is traced on the nonlinearity images.

The average values of shear modulus μ and nonlinear parameter γ for each lesion individually are reported in Tables III and IV, respectively. These tables also contain the mean values and the standard deviations (STDV) computed for all five fibroadenomas and invasive ductal carcinomas. Statistical analysis of these indicates that there is no significant difference between the means of the shear moduli for the FA and IDC. Statistical analysis of the nonlinear parameters γ , however, shows the means are different between the populations of the FA and IDC (difference in means = 26.7 [7.6–46] 95% confidence level [49]). A test of the variance ratio indicates the populations have the same variance, which is estimated to be 81. Based on this, one may (crudely) estimate that 93% of all FA have a nonlinear parameter lower than 20.6, while 93% of all IDC have a nonlinear parameter higher than 20.6. The material property values for each tumor are also presented in Fig. 11, where we plot each tumor in the shear modulus-nonlinear parameter plane. This plot and the tables clearly illustrate that the value of the nonlinear parameter, γ , is much higher for invasive ductal carcinomas than for fibroadenomas, while the shear modulus displays no clear trend.

IV. Discussion

Many of the modulus reconstructions shown here exhibit artifacts near their boundaries. Based on several years of experience with plane stress, plane strain, and 3-D modulus reconstructions, we recognize these as due to inaccuracies in our assumed boundary conditions [50], [51], [34], and [48]. The plane stress assumption tends to keep these artifacts confined to the boundaries. Nevertheless, improvements in our handling of boundary conditions is an area of active effort.

Statistical analyses of the results in Tables III and IV indicate that the shear modulus μ is not significantly different between fibroadenomas and invasive ductal carcinomas. This finding is consistent with the results of strain imaging [11]–[13], [19], which show that there is no significant difference in strain image contrast between fibroadenomas and invasive ductal carcinomas.

The shear modulus contrast was found here to be in the range from 4–22. This is to be interpreted as the ratio of the modulus of the lesion to the *minimum* modulus of the background. This interpretation allows us to compare the range of values reconstructed here to those in the literature. The *ex vivo* measurements of [26] give an expected contrast in the range 4–6, while those in [29] give a range 2–15. These measurements were made in quasistatic compression. Most *in vivo* values reported in the literature come from dynamic methods. Contrasts measured by MRE at 100 Hz range from about 3–7 [52]–[54]. Contrasts inferred by measuring broadband shear wave time-of-flight range roughly 3–20+ [55]. What little consensus there appears to be in the literature regarding shear modulus contrast in these tissue properties is consistent with the findings here.

Statistical analyses of the results in Tables III and IV indicate that the nonlinearity γ is significantly different between the populations of fibroadenomas and invasive ductal carcinomas (difference in means = 26.7 [7.6–46] 95% confidence level [49]; difference persists at 99% confidence level). That this is the case is consistent with the implications of quantitative *ex vivo* measurements reported in [26], [27], [29].

We know of no published *in vivo* data for the nonlinearity parameter of these breast tissues against which we can compare. Fitting the *ex vivo* data of [26] to a modified Veronda–Westmann model as used here gives a nonlinearity of $\gamma \approx 1.3$ for the fibrous tissues reported there, and a $\gamma \approx 7$ for IDC. These may be compared to the average values found here, for a fibroadenoma $\gamma \approx 7$, and for an IDC $\gamma \approx 34$. In both cases, the values found here are about five times higher, indicating that the observed nonlinear response seen here is stronger than

predicted by the measurements of [26]. We note that the Veronda–Westmann model used in [29] is different from that used here, and so a direct comparison of those parameters to ours is inappropriate.

All ultrasound echo data used in this study were acquired using a 1.5D linear array transducer. Consequently, out-of-plane tissue motion and/or subtle changes of the image plane associated with free hand motion could potentially result in large tracking errors due to significant signal decorrelation. However, we attempted to minimize these errors in two ways. First, the ultrasound data were acquired under the guidance of a real-time strain imaging system [13]. With this, we attempted to maintain a constant imaging plane by using the real-time feedback to the eye-brain system. Second, the “displacement quality metric” [36] is an empirical method to actively filter out low quality displacement data that may have suffered from large out-of-plane motion.

A number of other factors in the data collection protocol give reason to interpret the present quantitative results with caution. Here we took advantage of a database that provides a convenient source of high quality *in vivo* displacement data. Nevertheless, the data were collected under suboptimal conditions to infer mechanical properties. Such limitations might be overcome relatively easily in future studies. These include the 2-D nature of the data, the lack of measured force to calibrate the modulus, the limited overall applied strain, and the lack of a standardized preconditioning protocol. Of these, the most obvious potential source of error is the use of the 2-D plane stress approximation in analyzing what is undoubtedly a 3-D deformation. This bias is discussed in [48], [56], [40]. The lack of a force calibration allows us to reconstruct a relative shear modulus only. In one image, therefore, the lesion stiffness is measured relative to one tissue, while in another, the lesion stiffness is measured relative to a different tissue. Hence, variations in lesion modulus contrast may be due as much to background variations as lesion variations. The analysis in [31] (56) implies that for the average parameters observed here, 10% overall strain is adequate to observe nonlinear effects above the noise level for a strain SNR of about 100. A strain SNR of about 10 requires an overall applied strain of closer to 30%. Hence, one might expect significantly more accurate γ reconstructions from an overall applied strain higher than the 12% value used here. Finally, we note that no standardized preconditioning protocol was followed, and this will result in an additional source of variability in the results. Considering these potential sources of variability, it is remarkable that the nonlinear effect is strong enough to distinguish the means at the 99% confidence level found here.

The interface between the lesion and background receives no special treatment in our approach. We treat the whole of the interior of the region of interest as a connected elastic continuum. This means that the displacement and traction (stress) variables are continuous throughout. In this model, slipping between fascia can be represented by a thin layer of very soft material separating the two fascia. In principle, our approach is capable of reconstructing such thin layers if the data suggest it is there. In practice, however, regularization tends to smooth over such sharp dips in the reconstructed modulus. Hence, the absence of such dips in the results indicates that they are not indicated by the data over and above other fluctuations (e.g., noise) in the measurements.

We modeled the nonlinear tissue response using a pseudo-elastic assumption and a modified Veronda–Westmann strain energy function. The use of the modified Veronda–Westmann strain energy function, as opposed to other strain energy functions such as Yeoh or Arruda–Boyce, is likely not a source of significant error. Over the relatively small strain ranges as used here, all these models can qualitatively and quantitatively reproduce the nonlinear behavior observed here. Furthermore, the use of only one large deformation field obviates

the possibility of discriminating one kind of model from another. Hence, we would not expect significantly different results from using a different strain energy function.

As suggested in [11], lesion area ratio has been found in other studies to be a strongly discriminating feature between benign FA and malignant IDC in strain images. This study, however, was not designed to quantitatively compare image sizes of lesions in different modalities. First, the spacial resolution of the modulus reconstructions was relatively coarse compared to both the strain images and B-mode images. Secondly, the precise shape and steepness of the boundary is also dependent upon the strength of the regularization parameter selected. Finally, an objective method to determine lesion boundaries to facilitate the comparison was not readily at hand. Nevertheless, we feel it appropriate to make one intriguing, albeit subjective, observation about lesion area. We note that not only is the nonlinearity γ elevated in every IDC, but γ tends to be elevated well outside the region of elevated shear modulus μ . That is, for the majority of the IDC in this study, γ is elevated well beyond the yellow curves delineating the region of elevated μ .

While every invasive ductal carcinoma has a nonlinearity γ greater than or equal to 20, only one fibroadenoma in the study has a nonlinearity γ larger than 10. Furthermore, a statistical analysis of the nonlinearity γ values for the fibroadenomas indicates that this straggler might safely be disregarded as an “outlier.” Given our small sample, however, it was nevertheless included in all our calculations.

It is tempting to try to explain the clear and striking difference in the nonlinear behavior of benign and malignant tumors in terms of the microstructural arrangement of structural tissue proteins. The second harmonic images of breast tissue collagen reported in [57] give us some indication of the microstructural differences between benign and malignant breast tumors. In the case of benign tumors it has been observed that the collagen bundles are significantly curved and have a large value of tortuosity, τ , defined as the ratio of the length of a fiber to the distance between its ends. This is in contrast to the fiber bundles observed in malignant tumors which are less curved and have smaller values of tortuosity [57]. If a given fiber bundle is stretched to a value that is less than or equal to its tortuosity ($\lambda < \tau$) it offers very little resistance since it deforms merely by straightening and not by increasing its length. On the other hand for a stretch greater than the value of tortuosity ($\lambda > \tau$) it can deform only by increasing its length and thus it offers significantly higher resistance. Because of this effect, a material embedded with fibers of tortuosity τ will have a force-deformation or a stress-stretch curve that has small slope for stretches less than τ and a larger slope for stretches greater than τ . Since the value of τ is smaller for malignant tumors than for benign tumors, the former will exhibit an earlier onset of nonlinear behavior than the latter, thus leading to a higher value of τ .

The results described in this paper provide an initial indication of the utility of nonlinear elasticity imaging in diagnosing breast cancer. These reconstructions may, however, be improved in the following ways. 1) The boundary conditions assumed for the forward problem most likely do not exactly conform to the physical situation. In order to address this we are working on a solution strategy that does not require any knowledge of the boundary conditions. 2) The plane stress approximation is clearly a source of error that could be overcome with the measurement of displacement in a 3-D volume. 3) Force and/or pressure calibration would improve shear modulus quantification. 4) A total of 12% compressive strain is barely sufficient to pry out the nonlinear behavior of tissue. A more reliable reconstruction of nonlinearity γ may be obtained by compressing the tissue to higher levels of overall strain (say 25%). 5) Variability in results can likely be reduced by following a standardized preconditioning protocol.

We note that this method is capable to reconstruct tumors of very small sizes. Even after downsampling the displacements by a factor of four we are able to detect tumors with width of only 5 mm (see Fig. 5). This points to the potential of shear modulus and nonlinear parameter images in detecting tumors in relatively early stages and thus improving the prognosis of breast cancer.

V. Conclusion

We have analyzed a set of ten patients with breast lesions using nonlinear elasticity imaging. The displacement field during a gentle free-hand compression was determined using radio-frequency ultrasound data. The compression achieved overall strains on the order of 12%. The displacement field at small strain was used to create shear modulus images and the displacement field at large strain was used to create images of the nonlinear elastic parameter γ , which represents rate of increase of stiffness with increasing strain. In doing so, the tissue was modeled as an incompressible hyperelastic material in a state of plane stress.

It was found that the tumors could be clearly located in the shear modulus images. These images, in conjunction with B-mode ultrasound images, were used to determine the spatial extent of the tumor. The average values of the nonlinear parameter within the tumor revealed that malignant tumors exhibited a stronger nonlinear response than benign tumors. The observed behaviors are consistent with micromechanical explanations based on the tortuosity differences of collagen fiber bundles in malignant and benign tumors. Using the average value of the nonlinear parameter as a diagnostic tool we were able to correctly classify nine out of ten tumors as either benign or malignant.

Future work in this direction includes collecting data and performing reconstructions in three dimensions, which would improve displacement estimation by accounting for motion in the elevational direction and also eliminate the plane stress hypothesis. It would also be desirable to measure displacements at larger values of overall strain, say around 25%, so that the nonlinear tissue behavior is more apparent.

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Fig. 1.

Fibroadenoma 1: (ROI 21 mm $\times$ 29 mm). (a) Upper left: B-mode extracted from near beginning of compression sequence. (b) Upper right: Strain image from near beginning of compression sequence. Stiff FA appears dark, showing low strain, with strong contrast against more compliant normal tissue. The low strain along the top, to the left and right of the lesion, is likely due to stress shielding from the stiff inclusion. (c) Lower left: Linear elastic shear modulus, μ . Stiff FA appears white with strong contrast against dark more compliant normal tissue. Yellow outline drawn to facilitate comparison between images. Note high degree of (negative) correlation between reconstructed stiffness and tissue strain. (d) Lower right: Tissue nonlinearity γ . The yellow outline corresponds to that shown in the μ image. The lack of contrast implies that the FA is not significantly more or less nonlinear than the background normal tissue.

Fig. 2.

Fibroadenoma 2: (ROI 16 mm $\times$ 30 mm). (a) Upper left: B-mode extracted from near beginning of compression sequence. This shows two lesions. (b) Upper right: Strain image from near beginning of compression sequence. The larger of the lesions seen on B-mode shows significantly less strain than the smaller. Again, a low strain stress-shielding artifact appears along top edge, to the right and left of the lesion. (c) Lower left: Linear elastic shear modulus, μ . The larger lesion, outlined in yellow here, appears stiffer than both the smaller lesion and the background. The smaller lesion to the left of the larger, seems to have a moderately stiff shell surrounding a compliant core. The region of apparently high stiffness on the top right corner corresponds to the region of anomalously low strain in (b). (d) Lower right: Tissue nonlinearity γ . The yellow outline corresponds to that shown in the μ image. This is the only FA that shows a significant nonlinear response, as indicated by elevated value of γ within the yellow contour.

Fig. 3.

Fibroadenoma 3: (ROI 14 mm × 25 mm). (a) Upper left: B-mode extracted from near beginning of compression sequence. (b) Upper right: Strain image from near beginning of compression sequence. Stiff FA appears dark, relatively small compared to the B-mode lesion. Region of low strain extends up toward skin surface. (c) Lower left: Linear elastic shear modulus, μ . Stiff FA appears white with strong contrast against dark more compliant fatty tissue. Overall stiffness contrast is lowest of all lesions in the study. (d) Lower right: Tissue nonlinearity γ . The yellow outline corresponds to that shown in the μ image. The lack of contrast implies that the FA is not significantly more or less nonlinear than the background normal tissue.

Fig. 4.

Fibroadenoma 4: (ROI 20 mm $\times$ 31 mm). (a) Upper left: B-mode extracted from near beginning of compression sequence. (b) Upper right: Strain image from near beginning of compression sequence. Stiff FA appears dark, showing low strain. Stress shielding artifacts at the top are again apparent. (c) Lower left: Linear elastic shear modulus, μ . Stiff FA appears white exhibiting markedly high stiffness. (d) Lower right: Tissue nonlinearity γ . The yellow outline corresponds to that shown in the μ image. The lack of contrast implies that the FA is not significantly more or less nonlinear than the background normal tissue. The region of enhanced nonlinear response at the left end of the lesion may be an extension of the stress shielding artifact from the upper left corner, as we have seen before, or may be due to slipping between lesion and background tissue, or due to the tissue itself.

Fig. 5. Fibroadenoma 5: (ROI 17 mm $\times$ 27 mm). (a) Upper left: B-mode extracted from near beginning of compression sequence. (b) Upper right: Strain image from near beginning of compression sequence. Stiff FA appears dark, showing low strain. Stress shielding artifacts at the top are again apparent. (c) Lower left: Linear elastic shear modulus, μ . Stiff FA appears grey, exhibiting moderately high stiffness. (d) Lower right: Tissue nonlinearity γ . The yellow outline corresponds to that shown in the μ image. The lack of contrast implies that the FA is not significantly more or less nonlinear than the background normal tissue.

Fig. 6.

Invasive Ductal Carcinoma 1: (ROI 21 mm $\times$ 31 mm). (a) Upper left: B-mode extracted from near beginning of compression sequence. (b) Upper right: Strain image from near beginning of compression sequence. Stiff IDC appears dark, showing low strain. Region of low strain appears wider than lesion in B-mode. (c) Lower left: Linear elastic shear modulus, μ . Stiff IDC appears white, showing markedly high stiffness. (d) Lower right: Tissue nonlinearity γ . The yellow outline corresponds to that shown in the μ image, which is the region of high shear modulus. The white region denotes high nonlinearity γ , which represents very strong nonlinear behavior. We note that the region of high nonlinear response extends well outside the yellow boundary.

Fig. 7.

Invasive Ductal Carcinoma 2: (ROI 15 mm $\times$ 32 mm). (a) Upper left: B-mode extracted from near beginning of compression sequence. (b) Upper right: Strain image from near beginning of compression sequence. Stiff IDC appears dark, showing low strain. Region of low strain appears wider than lesion in B-mode. (c) Lower left: Linear elastic shear modulus, μ . This IDC shows moderately high, inhomogeneous stiffness distribution. (d) Lower right: Tissue nonlinearity γ . Like the other IDC, the lesion shows high nonlinearity γ , which represents strong nonlinear behavior. We note that the region of high nonlinear response extends well outside the yellow boundary. The apparent nonlinear response along the bottom edge may be due to processing artifacts.

Fig. 8.

Invasive Ductal Carcinoma 3: (ROI 19 mm $\times$ 32 mm). (a) Upper left: B-mode extracted from near beginning of compression sequence. (b) Upper right: Strain image from near beginning of compression sequence. Stiff IDC appears dark, showing low strain. Region of low strain appears wider than lesion in B-mode. (c) Lower left: Linear elastic shear modulus, μ . This IDC shows moderately high, inhomogeneous stiffness distribution. (d) Lower right: Tissue nonlinearity γ . Like the other IDC, the lesion shows high nonlinearity γ , which represents strong nonlinear behavior. We note that the region of high nonlinear response extends well outside the yellow boundary.

Fig. 9.

Invasive Ductal Carcinoma 4: (ROI 20 mm $\times$ 30 mm). (a) Upper left: B-mode extracted from near beginning of compression sequence. (b) Upper right: Strain image from near beginning of compression sequence. Stiff IDC appears dark, showing low strain. (c) Lower left: Linear elastic shear modulus, μ . Stiff IDC appears white, showing markedly high stiffness. (d) Lower right: Tissue nonlinearity γ . The yellow outline corresponds to that shown in the μ image. The nonlinear response is again elevated in the lesion. It does not extend all the way to the yellow outline on the left, but extends well beyond it to the right. The apparent nonlinear response along the bottom edge may be due to processing artifacts, or may be real tissue response.

Fig. 10.

Invasive Ductal Carcinoma 5: (ROI 26 mm $\times$ 32mm). (a) Upper left: B-mode extracted from near beginning of compression sequence. (b) Upper right: Strain image from near beginning of compression sequence. Stiff IDC appears dark, showing low strain. Region of low strain appears wider than lesion in B-mode. (c) Lower left: Linear elastic shear modulus, μ . This IDC shows moderately high, inhomogeneous stiffness distribution. (d) Lower right: Tissue nonlinearity γ . Like the other IDC, the lesion shows high nonlinearity γ , which represents strong nonlinear behavior. Because this lesion nearly fills the lateral extent of our field-of-view, it is difficult to judge whether the region of high nonlinear response extends well outside the yellow boundary to the right.

Fig. 11.
Averaged elastic parameter values within the tumor region.

TABLE I

Mesh Parameters For FA

	FA 1	FA 2	FA 3	FA 4	FA 5
nodes in axial $\times$ lateral	36×39	27×41	24×34	35×47	29×37
# of nodes	1404	1107	816	1645	1073
# of elements	1330	1040	759	1564	1008
area in mm^2	597.5	467.2	341.0	638.9	452.8
grid spacing axial $\times$ lateral (mm)	0.599×0.75	0.599×0.75	0.599×0.75	0.599×0.682	0.599×0.75

TABLE II

Mesh Parameters For IDC

	IDC 1	IDC 2	IDC 3	IDC 4	IDC 5
nodes in axial $\times$ lateral	36×42	26×43	33×43	34×41	45×43
# of nodes	1512	1118	1419	1394	1935
# of elements	1435	1050	1344	1320	1848
area in mm^2	644.7	471.7	603.8	593.0	830.2
grid spacing axial $\times$ lateral (mm)	0.599×0.75	0.599×0.75	0.599×0.75	0.599×0.75	0.599×0.75

TABLE III
Shear Modulus μ And Nonlinear Parameter γ For Each FA (Average Of 20 Samples Within Each)

	FA 1	FA 2	FA 3	FA 4	FA 5	Mean	STDV
averaged μ	22	6.5	4	17	9	11.7	6.7
averaged γ	5	19.5	6.5	2.5	3	7.3	6.3

TABLE IV
Shear Modulus μ And Nonlinear Parameter γ For Each IDC (Average Of 20 Samples Within Each)

	IDC 1	IDC 2	IDC 3	IDC 4	IDC 5	Mean	STDV
averaged μ	22.5	7.5	7	22	14.5	14.6	6.6
averaged γ	47	41	34	28	20	34	9.5