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We are progressing well toward the original goals delineated in the grant. The MR sequences have been written to measure vibrations in all three directions. No attenuation of the vibration can be observed across a homogeneous sample. No vibration is seen in directions perpendicular to the induced vibration. These two results suggest that a simple linear model is appropriate. A linear model allows the elasticity to be calculated directly without elaborate calculations. This is encouraging. We have written and tested code to calculate the elasticity from measured phase changes assuming a linear model for the vibration. However, the phase changes used to calculate the vibrational displacements are relatively small using our current apparatus. Therefore, we are concentrating on increasing the phase changes by increasing the amplitude of the vibration and the strength of the magnetic field gradients. We have made significant progress toward the original objectives of this grant and we have accomplished some of the objectives for the second year of the grant such as measuring attenuation and scatter.

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John Ware 6/30/97

PI - Signature Date

## Table of Contents

# MR Measurement of Breast Tissue's Anisotropic Mechanical Properties: Breast Cancer Detection and Classification

## Introduction:

We are developing a magnetic resonance (MR) method of measuring the mechanical properties of tissue, including the hardness, quantified by the three dimensional (3D) modulus of elasticity, and the density. Tissue is vibrated at low frequency and the displacement of the tissue will be measured with MR imaging. The mechanical properties of the breast will be calculated from the measured displacements via a differential equation describing the motion. We will measure the elasticity in all three directions by vibrating the tissue and measuring the resulting three dimensional displacement. Measuring the 3D elasticity is important because the anisotropic distribution of fibrous tissue in the breast suggests that the elasticity will be anisotropic. In addition, we will test for nonlinearities and make sure that the measured displacements are consistent with the linear lossless wave equation; if it is not we will find the non-linearities most consistent with the data.

Elasticity measurements can play several roles in breast cancer detection and in evaluating treatment effectiveness. Elasticity may help classify lesions identified with mammography which is sensitive but not specific; roughly two thirds of the lesions detected with mammography turn out, on biopsy, to be neither malignant nor pre-malignant [1]. Secondly, because mammography can not detect all palpable lesions [5 ,2], elasticity measurements could supplement the physical examination and mammography in screening programs. The sensitivity of mammography with current technology is between 85% and 90% [3]. Elasticity measurement should be used as part of the screening examination if it catches some significant fraction of the missed malignancies. Abnormalities such as architectural distortions which are often missed in mammography [4] should be well visualized with elasticity measurements. We are developing 3D elasticity measurements to determine its usefulness in classification and screening. Once tissue properties are measured for a variety of tumors and benign lesions, less expensive methods can be developed that are designed to measure the relevant tissue properties.

Several different types of imaging techniques are being explored to supplement mammography: Doppler ultrasound [5,6], MRI contrast studies [7,8,9], radio nuclide uptake [10], and electrical impedance imaging [11]. We feel attempts to measure the elasticity of breast tissue are the most promising. Hardness or elasticity has a strong correlation with cancer. The physical examination is an important part of breast cancer screening [12,13,14,15,16]. In the Breast Cancer Detection Demonstration Project, around a third of malignancies were found with physical examination and not with mammography [17]. It is reasonable to look for similar changes in smaller lesions. There have been four approaches to measuring elasticity using ultrasound. None is capable of measuring anisotropic elasticity and all have significant practical problems in implementation. The first technique changed the compression and measured the resulting distortion

[18,19]. The second technique uses low frequency sound to vibrate the tissue and Doppler ultrasound to identify regions with large peak velocities [20,21,22,23,24]. Preliminary measurements of the "sonoelasticity" of masses in rodents and prostatectomy specimens have indicated that it correlates well with malignancy [7 ,28,25]. The third technique, ultrasonic computed tomography [26], measures the speed or attenuation of ultrasound. The fourth technique measures low frequency shear wave amplitudes with MR [27]. Obtaining quantitative measurements of tissue elastic properties from this technique is problematic because of attenuation and dispersion of the shear wave [28, 29]. Low frequency transverse waves are not attenuated or significantly dispersed over the thickness of the breast.

However, little quantitative work has been done studying the mechanical properties or behavior of soft tissue. Heart wall, heart valves and cartilage show anisotropic elasticity [30,31,32,33]. Aortic valves have also shown viscoelastic properties [34]. However, no systematic studies have been made to identify the appropriate models for soft tissue such as breast tissue. Such information would be important for detecting and classifying lesions and in breast reconstructions.

Therefore, we have been developing methods of studying vibrational motion of breast tissue. We have implemented an MR imaging technique to measure the displacement of tissue during periodic vibration. The linear, elastic model can be used for anisotropic material if the elasticity is measured in all three directions. This is important because the elasticity of breast tissue is probably anisotropic; the fibrous tissues in the breast tend to be oriented. However, if viscous or attenuation effects become important, the measured value of elasticity will be different when measured in different environments. In this case, accurate estimates of the elasticity might still be made using the measured displacements and a finite element model of the correct equations of motion [35].

Our long term hypothesis is that elasticity measurements will 1) contribute toward the accurate classification of lesions detected with mammography and 2) detect a significant number of the malignancies missed by mammography. The hypothesis we are testing in this proposal is that we can measure the mechanical properties of tissue with MR using a linear, lossless motion model. We are also establishing that the properties measured completely describe the vibration of tissue so there is no other information to be gained from measurements of vibration. This is important to establish before trials with patients are started so the correct measurements are made.

The specific technical objectives we planned for the first year of this project were: 1) Refine the MR measurement of three dimensional displacement during vibration. 2) Compare the elasticity calculated from the MR displacements with a linear model to known elasticity's for isotropic and anisotropic materials.

Some of the objectives from the second year were also accomplished: Measure motion perpendicular to the direction of forced vibration. Measure viscous losses by the attenuation of the vibration across the material.

**Body:**

The first objective of this grant was to refine the MR measurement of three dimensional displacement during vibration. The first element of the objective was to rewrite the MR sequence we used to obtain displacements. We improved the timing and added motion sensitizing gradient pulses in all three directions so we can measure displacement in all three directions. We are also moving from a GE 4.8 machine to a GE 5.x Epic machine which required rewriting the sequences.

The second element necessary for the first objective was reducing the noise fed into the MR from the audio system that powers the piezoelectric crystal vibrating the sample. We have been able to reduce the noise to levels below the ambient noise without reducing image quality; this is a reduction of almost an order of magnitude. The signal to noise ratio (SNR) of motion sensitized images is now the same as that of standard images using the same imaging parameters. A series of incremental improvements were required. A better audio amplifier reduced the noise somewhat. The transformers used to couple the amplifier to the crystal can be used to filter out most of the remaining audio amplifier noise. Shielding the leads of the secondary winding of the transformer reduced the noise further. The final step was isolating the coaxial shields from the audio circuit and grounding them to the room itself. Grounding always seems to be somewhat of an art. It is much simpler to put a shield around the crystal itself but the shield produces eddy current artifacts in the images which are difficult to isolate from the sample.

The final element of the first objective was increasing the power of the system which was relatively easy. We have increased the voltage and power of the system.

The second objective we set was to compare the elasticity calculated from the MR displacements with a linear model with known elasticity's for isotropic and anisotropic materials.

The first element of this objective was to measure displacement amplitudes along to the direction of the induced motion and perpendicular to the direction of the induced motion. The displacements were measured and they are consistent with a linear model. We do not observe any change in the magnitude of the displacement across a homogeneous sample. This is a good indication that the system is indeed linear. We see no motion in directions perpendicular to the induced vibration. To measure the displacement with sufficient accuracy, we had to average over many pixels. To study the amplitude of the displacement along the direction of the induced vibration, we averaged pixels along lines perpendicular to the induced motion. To look for motion perpendicular to the induced motion, we averaged pixels along lines parallel to the induced motion. We need to increase our sensitivity.

The second element of the second objective was to calculate the elasticity from MR displacement measurements. Code was written in MATLAB to calculate the elasticity from a series of images taken with different lags between the motion and the motion sensitizing gradients.

At least two lags are needed to calculate the displacement; we use more at present to increase SNR's. Simulations were run to check the code and study sensitivity.

The phase differences induced by vibration are used to calculate the elasticity. Those phase differences are proportional to the product of the displacement and the gradient strength. The combination of gradients and displacement we are now able to generate experimentally produces approximately one degree phase changes. By averaging several hundred pixels we can obtain reasonable accuracy but averaging can not be used for inhomogeneous materials and limits the accuracy of the results for homogeneous samples.

Therefore, we are working to increase both the gradient field strength and the displacement. We have limited amounts of data using an add on head coil with twice the gradient strength we have on the stock MR. The coil is designed for functional magnetic resonance of the brain by Advanced NMR Systems. The data is better but not good enough. Therefore, we are in the process of porting the MR sequence to a small bore MR imager made by SMIS that has gradients that are 20 times as strong as those on the clinical system. We are making a vibrational system small enough to fit into the small bore system.

We are studying three methods of increasing the vibrational displacement in the clinical MR: A bimorph piezoelectric element has sufficient displacement but the force is only sufficient for small samples (50 grams). A bimorph is a two piezoelectric elements bonded together with opposite polarities so when one is expanding the other is contracting. A positive voltage flexes the pair into an arc and a negative voltage flexes the pair into an arc the other direction. The second option is a stacked piezoelectric actuator with many elements; the displacement of each element is independent of thickness so many thin elements produce a much larger displacement. However, a lever arm would be needed to increase the displacement to desired levels. This kind of actuator has sufficient force and displacement if the lever arm can be made strong enough. The third option is a pair of rotating shafts on either side of the sample. Each shaft would have a slightly off center or bent segment that pushes the object back when they were rotated. The shafts would be rotated with an electric motor. This option provides sufficient force and displacement but the materials might have to be constructed from stainless steel which might cause eddy current artifacts that are too large. The size of the eddy current artifacts will depend on how we couple the shafts to the sample. We are doing experiments to see how strong we can make the lever for the piezoelectric actuator and how well we can isolate the shafts from the sample.

The lack of sufficient displacement with piezoelectric crystals can also be solved by working at resonance frequencies where the displacement is more than an order of magnitude larger than when driven at low frequencies. The currently used technique accumulates phase in the MR image by following the displacement with the gradient waveform. Because the gradients can not follow displacements that are

faster than 1kHz, we are looking at other mechanisms to detect the higher frequency displacement. We have simulated periodic displacement at higher frequencies during an RF pulse. The simulations show reduced amplitudes of magnetization that reaches the transverse plane resulting in reduced signal amplitude. The reduction is nearly independent of the frequency of the displacement. The reduction in signal is not linear with displacement but it is monotonic so the displacement can be estimated from the signal reduction. We are now designing RF pulses to increase the magnitude of the signal reduction to usable levels. These results suggest that high frequency displacement during the RF pulse is measurable. Therefore, piezoelectric crystals can be used to induce measurable displacements at resonance. The intriguing aspect of this technique is that the properties of the tissue as a function of frequency can be studied.

We are also working on a related project that is not being funded by this grant. We are developing an elastic image alignment algorithm. We are planning to use our image alignment algorithm to measure static displacements. This would allow the elasticity to be estimated using a few assumptions as other groups have been doing [17,18].

However, our primary efforts are directed toward measuring the low frequency displacement with the method described in the original proposal by increasing the gradients and displacement.

**Conclusions:**

We are progressing well toward the original goals delineated in the grant. The issues have changed slightly as problems we did not foresee were more problematic than the problems we foresaw. However, we have made significant progress and accomplished some of the objectives for the second year of the grant such as measuring attenuation and scatter.

Our results suggest that a linear model is appropriate to calculate the elasticity from transverse vibration of materials at low frequencies. Attenuation of the displacement is negligible throughout the sample and there is no measurable vibration perpendicular to the induced vibration. Therefore, this method should provide a good way to measure elasticity simply and accurately because the linear model allows the elasticity to be calculated directly without elaborate analysis.

We are developing methods of generating larger displacements in the MR to increase the sensitivity of the method.

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