Ultrasonic Tissue Characterization

At the Sendai Symposium on Ultrasonic Tissue Characterization, in-depth, up-to-date reports were presented by leaders in the field. The methods covered were image processing, scattering, elastography, spectroscopy, and microscopy from the perspective of engineering developments, limitations, and clinical applications. Many tissue types were examined, including the liver, myocardium, integumentum, and vascular structures. The informative discussions following each presentation are reproduced in this volume, capturing the spirit of the symposium.
Chapter 7


The medical motivations for looking into imaging of tissue elasticity are listed below:

- In many cases, a relationship exists between the presence of pathology and the palpable elastic properties of the tissue (e.g., breast, prostate, liver);
- Many breast and prostate cancers are routinely detected by palpation. Such cancers may or may not be seen by ultrasonic imaging;
- Detection by palpation is limited to relatively large, proximal hard nodules;
- Information contained in images of tissue elasticity cannot be obtained from any other diagnostic imaging modality.

In many cases a relationship exists between the presence of pathology and palpable elastic properties of tissues. For example, in breast cancer, a large percentage of breast cancers are detected by the patient. Many breast and prostate cancers are routinely detected by palpation. Such cancers may or may not be seen by ultrasonic imaging. It is another fact that many times you may not see such tumors with ultrasound or with mammography. Other times you can confuse what you see with benign lesions, for example, in the breast; some carcinomas look just like fibroadenomas. Detection by palpation, however, is limited to relatively large, proximal hard nodules. We have done many experiments where we

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Fig. 7.1 Summary of the literature on the measurement of elasticity of soft tissues

have hidden a hard nodule in a gel phantom, and we tried to palpate it from the outside, and in most cases you can not feel anything, even though the nodule that you put in the phantom might be quite hard and large. Finally, information that is contained in imaging of tissue elasticity cannot be obtained from any other diagnostic imaging modality. Even though this parameter appears to be quite fundamental, you cannot get to it using any other sophisticated modality.

7.1 Previous Works on Tissue Elasticity

Figure 7.1 shows the kind of work that has been going on in the world in the last ten years in this area. This area basically has to do with mechanical properties of soft tissues. There have been basically four parts. One has been to simply inspect images undergoing motion, and then try to glean from that information about hardness and softness of material. There are some parametric methods that have also been looked at since about 1982. Even before that, in 1978, several groups have looked at different parameters of motion but did not compute elasticity directly.

There have been some Doppler techniques which have used either internal
excitations or external excitation. In fact, internal excitations were deemed to be not strong enough to really get a good Doppler signal, but that could have been because of the wall filters that are in the machine that actually occlude this in favor of the motion from the blood. External excitations have been used by various authors here in the last five or seven years. Notably, the work at Rochester University by Lerner and Barker, where they have looked at relative hardness. They used a technique called sonoelasticity. There have also been some techniques in Japan—Yamakoshi and Sato, for example—and others which have attempted to measure the elastic wave velocity and relate that back to elasticity. Finally, we have a relatively large group of time domain correlation methods, which are subdivided into internal and external excitations. Using the internal excitation, investigators have looked at velocities and displacements of tissue as a function of the heart cycle, e.g. Dickinson and Hill, 1982, a fundamental paper. There were more papers from that group—e.g. Pistor, 1986 and 1988. In fact, 1982 was a productive year. Wilson and Robinson also have suggested that by using these time domain correlation methods, it might be possible to compute strain by looking at M-mode type information from internal excitation.

For time domain correlation due to external excitation, there have been some works going on in Japan in Tokyo—including our group since 1990, attempting to actually look at strain directly, and Young's modulus estimation from that. O'Donnell's group at Michigan has reported similar work in 1992.

The domain of our work is covered basically by the shaded boxes (Fig. 7.1), i.e. we are doing time domain correlation, using external excitation, and attempting to measure strain and Young's moduli.

**7.2 Theory**

If we measure the strain along a single axis then the expression for the estimation of $E$ (elastic modulus) is given as

$$E_1(x,y,z) = \frac{\sigma_{zz}}{\epsilon_{zz}} \left(1 - \nu \frac{\sigma_{xx} + \sigma_{yy}}{\sigma_{zz}} \right)$$  (7.1)

where $\nu$ is the Poisson’s ratio, $\sigma$ is the stress component on the element $(x,y,z)$ whose subscripts indicate direction and $\epsilon_{zz}$ is the strain component in the $z$ direction.

We can measure the strain along a single axis, and that is something which we are pretty much limited to, because the axis of the sound wave is where you have the maximum resolution. The other axes usually give very poor resolution, and when you attempt to incorporate off-axis information, you usually introduce more noise into the measurement than you can hope to gain. But in general, you can show from elastic theory based on some isotropic assumption that the estimation of the Young’s modulus, $E$, of any point in space $X, Y, Z$ (Fig.7.2), is possible. You have the transducer on top and you have the compressor on the

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Fig. 7.2 The geometry of Young's modulus estimation of a point in an elastic solid, showing all the components of the stress tensor.
of two we incur an error by making some homogeneous assumptions about the stress field, is not unreasonably large. I will show later some artifacts that are encountered due to that assumption.

7.3 Elastography

The end product of elastography is a new kind of image which we call an elastogram, which is basically a two-dimensional image of the strain distribution in the object. In order to get a real quantitative image of the Young's modulus, you need to know the stresses and the strains. The strains are estimated here, where you basically look at a family of a lines, which are actually RF echo lines, before you compress the tissue. You apply rapidly a very small compression to the tissue, (on the order of 1% or .5%) and look at a second set of RF a-lines. We pair them up and do cross-correlation analysis in order to estimate the time shift of one relative to the other. And that, as I will show you a little later, leads you to get values or estimates of the local strain in the image. The term "local" means on the order of a millimeter or so in extent. If we assume that the stress is constant everywhere, then there is an inverse relationship between strain and Young's modulus. Thus if you can estimate or make an image of the strains, you have basically an inverse image of the Young's modulus. However because this stress does change, as I will show you later, more work must be done. In order to get a handle on that, we do measure the applied stress to the whole system. We can use some of the models in the literature, namely, those of Love(1929) to give you some theoretical stress distributions in homogeneous materials. From that, we can estimate the absolute axial stress, and that means all three components of stress, as you have seen from the previous formula. We then plug them into the equations that we have used before, and from that we compute the Young's moduli. The final product, as I say, is the elastogram.

Figure 7.3 is a finite element analysis picture of stresses that are incurred under a compressor. This is greatly exaggerated in order to see the detail, because usually we are compressing just 1% or so. The compressor is at the top, and you can see that under the compressor you typically get a kind of decay of the stress. There are very high levels of stress at the compressor's corners. You will see those later from some simulation results. But as you go further down, it is fairly well behaved. There is also some side-to-side variation, resulting in a "mechanical beam" of stress. Figure 7.4 shows some examples that we published recently in UMB, where you have the theoretical model from Love in 1929. Figure 7.4(a) shows the theoretical values, where you can see this kind of beam-like behavior of the stress. Figure 7.4(b) shows some experimental results that we produced at the lab that basically show you a very similar kind of a pattern, with an rms error of about 18% between the theory and the experiment (Figure 7.4(c)).

Fig. 7.3 A finite element simulation of the stresses under a flat compressor. Note stress decay with distance and high stress levels under the corners of the compressor.

Fig. 7.4 The stress under a flat compressor (a) theoretical behavior using the formalism of Love(1929); (b) Experimental results; (c) RMS error between (a) and (b).
Fig. 7.5 The estimation of strain. The time delay between congruent windows in two (pre- and post-compression RF signals) is estimated by cross-correlation. This is repeated for a second pair of windowed signals. The difference between the two delays divided by the original timed interval between the windows is an estimate of the strain.

7.4 Basic Technology

As mentioned earlier, the strain is estimated from the ultrasonic wave form, and the way that is done is shown in Fig. 7.5. The figure shows a typical rf wave form, with two time gated windows. The centers of the windows are separated originally by some amount, \( \Delta T \). We then apply a compression to the whole system. What you typically observe is that there is some time shift, the sample will shift by a small amount, and that amount is measured by cross-correlation. The strain is actually estimated by looking at the difference between the new spacings and dividing this by the original spacing, and that will be the change in the size of the structure over the original structure, which if you assume a constant speed of sound, will then translate to the change in length of the structure over the original length, which is the longitudinal strength.

Figure 7.6 is typical cross-correlation function between the two signals. You can see that they are very close, and you are basically trying to estimate the time delay. What is also shown here is the sampling interval, \( \Delta t \). Even though I have plotted this as a continuous function, all we really have to work with are the samples. And so you have a problem: if the peak is really between the samples, how well can you tell where that peak was, because all you have available to you are the samples? (See Fig. 7.7.) We have looked at methods to estimate the peak.

Fig. 7.6 A typical cross-correlation function between two ultrasonic RF signals.

Fig. 7.7 Reconstructive interpolation method. Many new interpolated samples are generated in between the original samples by convolving the cross-correlation function with a sinc function.
of cross-correlation functions. There are basically two main techniques. One is to look at the actual digitized samples, and fit, for example, a parabola or a cosine or some such function to them. This works very well, it is very easy, but it produces large biases, so we have basically not used these methods much. What we use now is a reconstructive interpolation method (Fig. 7.7), where we filter the spectrum by a boxcar-type of filter, which is the same as doing a convolution in the time domain with a sinc function, and what that does is to create many new samples in between the original samples (upsample): what we are doing is simply creating additional samples in between so we can approximate the peak location very accurately. The reason this is important because we are looking at very, very small time shifts. If we were compressing a structure which is 10 cm in size by 1%, then the whole structure goes down by 1 mm, which has to be divided over approximately 500 pixels. This means that 2 micron motions must be detected accurately.

The lowest possible errors that you incur in time-delay estimation for the location of the peak is given by the \( \sigma_{CR} \), which is the Cramér-Rao lower bound for band pass signals. This is the best that you can do from a theoretical point of view. This lower bound is given in eq. (7.3), viz.

\[
\sigma_{CR} = \frac{1}{2\pi f_0 \sqrt{B \Delta T}} \quad (7.2)
\]

\[
\sigma_T = \frac{\Delta T}{\sqrt{12}} \quad (7.3)
\]

where the standard deviation of the error is inversely proportional to the center frequency \( f_0 \) and the square root of the signal to noise ratio \( SNR \) and the time \( T \) bandwidth \( B \) product. So if you plug in some typical numbers, for example, 50 MHz sampling frequency, 20 ns sampling interval, center frequency 5 MHz, bandwidth of 3.75 MHz and signal to noise ratio of 48 dB, then you get the Cramér-Rao lower bound to be 0.024 ns, which is the theoretical lower bound on the estimate. If you digitize the signal then your digitization uncertainty is known to be equal to the \( \Delta T \) to sampling interval over the square root of 12(eq.7.3). If you compute that for a 50 MHz digitization rate, you get a value of 5.7 ns. So you can see that the digitization noise, even at 50 MHz, will not let you attain the Cramér-Rao lower bound. This is again why you have to interpolate and be very careful how you do it, so that you can get close to the Cramér-Rao lower bound. Observe that interpolation is necessary even when the Nyquist criterion is met. Figure 7.8(a) shows the strain field under a flat compressor. Figure 7.8(b) shows the noisy elastogram; the noise is due to the uncertainty in strain estimation.

Figure 7.9 is the first elastogram we have produced. That noise is the result of your inability to exactly estimate time delay. When you put a tumor into an otherwise uniform area the effect can be explained on the basis of a one-dimensional model. If you look at the tissue as being composed of cylinders that

Fig. 7.8 Noise in the elastogram. (a) a simulated image showing the ideal strain under a flat compressor; (b) a noisy elastogram showing the noise added to the ideal strain distribution in (a) due to the uncertainty in time delay estimation.

Fig. 7.9 The first elastogram produced in our laboratory (1990). The target is a composite sponge phantom. (a) photograph; (b) sonogram; (c) elastogram.
Fig. 7.10 A simple model of tissue as composed of non-interacting, parallel elastic cylinders
do not interact with each other (Fig. 7.10), then Fig. 7.11 will show you what happens here.

If the Poisson's ratio is zero, then you do not have any lateral interaction, and that is easy to explain then. You have, for example, three cascade springs of original length script l, and you have the nodes A, B, C, and D. When you compress the system by some amount \( 2\Delta l \), then if you do some simple statics calculations you will discover that each one of these springs has now compressed down to a new length of \( l \), the original length, minus \( 2/3\Delta l \). If you sum up all the two-thirds \( \Delta l \), you get back your global reduction in size, \( 2\Delta l \). And if you plot the strain, the strain would then be the two-thirds \( \Delta l \), the change in the length over the original length. So it is two-thirds \( \Delta l \) over the \( l \) that you started out with. When you look at all those points now, A', B', C' and D', which correspond to depth, you basically get a constant strain. It simply tells you that all these springs are the same, and therefore they are all straining by the same amount (Fig. 7.12).

In Fig. 7.13, we show a case where we substitute one of these springs by a totally uncompressible spring. When we do the same experiment here, the very hard spring has an original length \( l \), and it will simply be shifted down, but its length will not change. The first and the last springs, which are the softer springs, will now all compress by a full \( \Delta l \), not two-thirds \( \Delta l \). So now the combined deformation has to be picked up by two of them instead of three. If you plot the strain going from A' to B', C' and D', you get the picture in Fig. 7.14 where the strain is high in the soft springs and it drops to zero in this case where you have a very hard spring, or an undeformable spring, and then jumps back up in the bottom spring. But observe that now the strain in the soft springs, is higher than it was before. So the strain alone does not really characterize the spring.

Fig. 7.11 A cascade one-dimensional spring model. All three springs have the same elastic modulus.

Fig. 7.12 The strain distribution in the springs of the previous figure. Note that the strain in all springs is equal.
Fig. 7.13  A cascaded one-dimensional spring model, where the central spring has been substituted by a totally rigid body.

Fig. 7.14  The strain distribution in the springs of the previous figure. Note that the strain in the rigid spring equals zero.

Fig. 7.15  Simulated strain images and elastograms of circular targets of various elasticity-constant levels.
7. Elastography: Imaging of the Elastic Properties

Figure 7.16 The clinical setup for elastography of the breast

Figure 7.15 shows images and elastograms in four elasticity contrast levels. These elastograms are simulated by putting many scatters in the locations of the finite element nodes and in between by interpolation, and then looking at what has happened to the rf as a result of compression, and producing elastograms from the rf signals. You can see that in both cases there are proximal and distal artifacts. In the images white is soft and black is hard. The presence of a soft structure produces hard front and back enhancements, and similarly, the hard structure produces proximal and distal elevated strain areas. The reason for that is that since you have a fixed deformation at the top, you may think of line-integrals going down vertically through the tissue here, and also through this "tumor". These line-integrals of the strains over the whole depth have to be equal to the total deformation. In other words, all line-integrals through all the strains in the vertical direction have to add up to the same displacement, because the integral of strain is simply the displacement.

We have constructed the system for the imaging of breast tissues, which involves a standard mammography machine onto which we have added a custom compressor (Fig.7.16). Figure 7.17 shows a custom mammography paddle. We have cut a hole in it, and we have put a standard 40 mm transducer array (a 5 MHz Diasonics transducer). It is driven by a stepping motor, which is computer controlled, and it can be swung out of the way so that you can take a mammogram first by putting the breast on the film cassette. You swing the transducer out of the way, get the mammogram, and then while the patient is still there and everything is stationary, you swing the transducer back, lock it into position over the breast, which now you can get to through an opening. By looking at the wet film and at these coordinates, you can look to see whether you have some suspicious area, and then you put the transducer over that and then you let this personal computer give the command to acquire the data from the Diasonics ultrasound machine, and then push the transducer down with this motor. Immediately afterwards, on the order of several tenths of a second, a second ultrasound picture is taken. The acquisition is done digitally by a LeCroy 50 MHz digitizer, and the data are then transferred to the PC. Currently, it takes 2 or 3 minutes to process an image, but that can be done much faster using various techniques. So we think that it should be possible to arrive at real time or near real time performance.

7.5 Results

Figure 7.0 is the very first elastogram we produced in 1990. Panel(s) is the optical image of the target. It is a sandwich composed of two kinds of sponges that are submerged in water. The harder sponge is the white one, and the softer sponge is the black one. This was done before the system that I described earlier was in existence. The scans were performed with a single element 3.5 MHz transducer in a standard water tank, and it took over half an hour. It produces a relatively poor quality sonogram and an elastogram. But it is quite evident that you get two different kinds of pictures. It turns out fortuitously that the contrast in echogeneity was on the order of 6 dB, and the contrast in elasticity as measured separately in the physics lab was about 5 dB. So that the sonogram and the elastogram are quite comparable as far as contrast. You can see the typical ultrasonic speckle in the sonogram. It is a little bit blocky because of the low resolution. On the right you see an elastogram, and here again the black does not signify anything about the echo strength. It now means hard. And the white now means soft. One thing that you immediately see is that it appears that the signal-to-noise ratio is improved. Indeed the signal-to-noise ratio in the elastogram is on the order of 4, whereas in the sonogram it is on the order of 1.0 or 1.7. You can see a darkening in the far field in the elastogram. This darkening, or "hardening" of the far field should not happen. We also get
Fig. 7.18 Diagonal cut sponge phantom (a) photography; (b) sonogram; (c) elastogram; (d) calibrated elastogram with correction for the ”target hardening” artifact.

the white line between sponges, which is a sort of softening effect. We did not initially understand either of these effects. In order to try to explain some of these artifacts, we constructed another phantom, which consisted of a simple block of foam which we have cut in half diagonally with an electric knife, and we have then joined the two halves together(Fig.7.18). There was nothing here other than a cut. Now what happens at the cut region is that the intact pores of the sponge are severed and all you have left there are tentacles that are sitting up from the bottom and down from the top. Evidently, that localized area of the sponge becomes much softer than the rest of the sponge. So when you do a standard sonogram you see nothing; you simply get a speckle field. But when you take the same data and produce the elastogram, you see the presence of the cut very clearly. So apparently, when we are looking at the previous phantom structure, there are two types of foam which have been cut by necessity, and that area where the cut has been made weakens the foam at the edges and produces this relative softening of the material, as you can see very nicely. The other thing you can see is the artificial darkening, which has to do with the fact that the stress does not remain uniform and in fact decays as you go away from the compressor. And so this stress decay or ”target hardening”, as we call it now, is basically an artifact which is similar in some sense to the attenuation-type appearance in sonograms. It is possible to correct for that fairly well, because we know what this function is from basic theory. A corrected one is shown in

Fig. 7.19 Breast cancer in vivo. The photo shows a cut surface (in the scan plane) of a breast carcinoma embedded in a tissue mimicking gelatin block which contains acoustic scatterers.

Fig.7.17(d). The numbers on the sides are numbers that relate to the Young’s modulus in the area, and they are given in inverse kilopascals. And the other thing that is informative about this particular picture is that you get some sense of the resolution of elastography as a function of depth. These pixels are 1 mm by 1 mm, so you see 1 or 2 mm type resolution in the focal area, and then you get some broadening in the far field and near field, similar to the ”hourglass” appearance of focused ultrasonic beams.

Moving on from phantoms to in vitro tissues, Fig.7.19 shows a cut piece of breast cancer that we have embedded in a tissue mimicking gelatin block that contains scatterers. We zoomed in on this area and produced a sonogram that you see on Fig.7.20 on the left, and the elastogram on the right taken from the same data exactly. We have added just enough scatterers to this matrix of gelatin so that the contrast between the tumor and the gelatin was quite low, almost nonexistent. You do get a strong reflection from the top of the tumor, due to the normal incidence from the acoustic impedance mismatch between the gel and the tissue, which is an ultrasonic artifact. This case is an illustration of the fact that you get little or no contrast echographically, but at the same time if you look at the elastogram, since this tissue turned out to be about five times harder than the surround, you get significant contrast.

Figure 7.21 shows our very first in vivo breast elastogram and sonogram pair. This is a craniocaudal sonogram of a normal breast. The image size is about 40 by 45 millimeters. This is a typical normal breast of a 42 year old volunteer. The dark proximal area is the subcutaneous fat, which appears also in the distal area. There are also different kinds of white and black areas. It is never really clear, for example, if a particular black area is fat, just like the subcutaneous
black area, or is it something else like a gland. If you look at the elastogram, one thing which is very apparent right away is that you get the subcutaneous fat, always the softest thing in the breast, showing up very well. The striking thing about this image is that it appears to have some regular structure of firm, rounded, or oval zones; you can count perhaps 10 or 12 of them. One does not see this kind of a structure in the sonogram, but perhaps there is only some suggestion of it. We think that these areas are consistent with the glandular structure of the breast, which is known to be firm.

The next image (Fig. 7.22) is a picture of the lower leg (sonogram and elastogram). I will show you several more breast lesions later, and I wanted you to appreciate the fact that you can practice elastography also in other small parts, such as muscle. One can see both parts of the gastrocnemius. In the sonogram, one can see the soleus muscle coming down and bending around in 90 degrees, and the flexor hallucis longus muscles is visible in the elastogram. And of course there are some fascia layers in between these muscles, which can be seen as well. In the elastogram, you get the gastrocnemius to show up very well. The soleus muscle can also be seen well. The flexor muscle appears quite harder than the soleus. You can see also see the fascia layers, which are supposed to be quite elastic. So there is good correspondence between the sonogram and the elastogram.

The next image goes back to the breast. We look at some pathology now. Fig. 7.23(e) is a mammogram of an 8 mm breast carcinoma. The sonogram and elastogram are in Fig. 7.23 (a) and (b). This is an unusual carcinoma in that it is hyperechoic, and it is also greatly shadowing. In the sonogram, you lose some information distal to the lesion due to the attenuation. Just like in the normal breast, we see a laminar fatty layer on the top. The tumor is sitting near the fat. You can see the sharp borders of the lesion. This particular cancer, as most of them are, is harder than the fat.

Figure 7.24 is another breast cancer. This is a 3 cm cancer. Figure 7.24(c) is a mammogram of this cancer in a 62 year old patient and (a) and (b) are the sonogram and elastogram, respectively. The sonographic appearance shows a large hyperechoic area. Quite uncharacteristically, you have quite a bit of enhancement behind this particular cancer. Most cancers will actually be shadowing. That is one of the signs that people usually look at. So this was not very well understood, and when we did the elastogram we made some interesting observations. First of all, the only hard thing that we saw appears to be a rim that goes around the tumor. You do not see much of it on the back side, but proximally, you see a hard, thin region. The internal part of this structure appears to be soft. Indeed, this was then proven to be a mucinous degenerated large carcinoma, which means that the internal parts of this carcinoma have necrotized, and they were now fluid-like and rather soft. So this was quite different than the other cancer that we saw before, which was uniformly hard. You now have something that appears to have an envelope, which is perhaps an actively growing area, and then you have the central area here which is soft. Observe also what happens to the fat layer, to which we never pay attention. Remember
Fig. 7.22  Images of the lower leg of a healthy male volunteer. (a)sonogram; (b)elastogram. G=gastrocnemius; F=fascia; FH=flexor hallucis longus; S=soleus

Fig. 7.23  An 8 mm breast carcinoma in vivo. (a)sonogram; (b)elastogram; (c)mammogram. Note the absence of shadows in the elastogram behind the hard, well defined lesion.
that in the previous cases the normal fat layer was laminar. In this case the fat layer, on what is left of it, is just two little pieces in proximal corners of the image. It looks like the tumor is invading it. By looking at what happens to the normal structure of the fat and in the presence of disease, we may get additional signs of malignancy.

The last case is a lesion that is quite irregular on the mammogram (Fig. 7.25(c)). It has different parts to it. The sonogram (a) shows a hyperechoic area. You cannot see the fat here very well either. If you look at the elastogram (b), it is interesting because you see a larger structure of hardness, and we are not sure exactly what that means. It could be that the dermoplastic reaction around the tumor, even though it does not show up on the sonogram, may in fact harden a larger area than just the tumor itself, and that may show up here. There may be some degeneration inside the lesion. And then we see another hard region to the left. The interesting part is that the fat layer that we had talked about, instead of going across it now goes down between these two parts of the tumor, and then comes back up. This is an abnormal morphology of the fat layer.

7.6 Conclusion

Elastograms are influenced by many factors, many of which we still do not understand. It certainly is influenced by the acoustics, as you have seen. It is also greatly influenced by the signal properties and the signal processing that we use, and we are just now beginning to learn how to do accurate time delay estimations under different conditions. I am beginning to learn how to do accurate time delay estimations under different conditions. What I did not mention is that the signal does not only shift in time, but it also distorts. That is why we keep the compression low (< 1%). When distortion occurs, the cross-correlation suffers greatly. So there are some methods and techniques to compensate for that, and those are actively being looked at. Similarly, the mechanics of the situation—the stresses and the strains—are also influencing the elastogram. And then there is some cross-talk among these parameters. So this is a very complex kind of a structure, and I believe we have enough work for many years to try to understand this, but I think you would agree that there is some potential here.

In conclusion, elastography is capable of imaging new tissue information in vitro and in vivo with reasonable sensitivity and resolution. It is possible to visualize elastic structures that are invisible on sonograms. Conversely, there are some cases where you can see things on sonograms that you cannot see on elastograms. Potential applications would include the breast, muscle, prostate and perhaps other small parts.
Discussion

NITTA: Thank you, Dr. Ophir. This paper is open for discussion. We can have a couple of questions.

ENDO: I'm Endo from Kanagawa University. Thank you very much for your nice presentation. I will speak in Japanese. This method that you have explained—you estimate the stress at the beginning, I would say. In using this in vivo, are you estimating the stress by means of the finite element method?

OPHIR: Estimating the stress using the finite element method? The answer is yes and no. We can estimate the stress from the fundamental theory, but that is limited to some rather special cases. And yes, you could measure it from some of the finite element models, as well.

ENDO: So in the case of living organisms, you can calculate stress. And can I understand that you are calculating stress without the use of finite element method?

OPHIR: Do you calculate the stress also there from finite element methods? All the pictures that I've actually shown you have basically used very simple stress models which are derived from Low's work, which basically assumes that the tissue, as I explained initially, is uniform. This is sort of similar to how you characterize an acoustic transducer. As you know, when you have a transducer, it simulates heterogeneous tissue. The sound field, as we have seen today, changes all over the place. But the manufacturer of the transducer always specifies in water or in homogeneous tissue, and then whatever errors are due to that we many times don't know about. We are doing something very similar here where we're characterizing our stress field either by finite element, by using the particular conditions of the situation, or from theory using the homogeneous assumption. As I mentioned, that causes errors or some artifacts, which in general are not bigger than a factor of two error in the resulting Young's modulus estimates.

THILLEN: First, I think that if you tried to estimate the time shift of two signals, you can only do that without a bias if the signals are identical. Otherwise, your correlation function will be biased. The second thing is that in one of your last slides you said that you confine or think you have to confine yourself to small organs. But I don't see any reason, a priori, why you shouldn't use the same method, for instance, for liver or any other kind of organ. Maybe it's a matter of applying a little bit more compression or whatever.

OPHIR: Yes, I agree that the time delay estimation that is usually described in the literature for using cross-correlation is just that. They're trying to look at two identical signals that are noisy and trying to estimate how far they have shifted from each other. And in our case, we do have distortions to the signal. Even if you only move by a very small amount, if it is speckled and not a deterministic target, the bandwidth will change and the spectrum will change, and the time domain appearance will change. And when you try to cross-correlate those two, you get a noisy estimate of time delay. So right now we are using small compressions, and the small compressions do several things. First of all, they make sure that that distortion is kept small, and therefore the bias in the
Elastography: Imaging of the Elastic Properties

cross-correlation function is small relative to the shift that you're trying to measure. It also assures, and that's something I didn't bring up in the paper, that there are no nonlinear effects of stress to strain relationships that we know very little about. But it is also known that under larger compression you might get changes in the Young's modulus due to those.

It's an interesting question about the size of the organs. There's no fundamental limitation here, except that what I didn't have to explain, that the decay of the stress under a compressor is relative to the size of the compressor. So if you have a very small compression—if you just push with your finger or with a small transducer—you will have a high stress field right underneath which will rapidly decay and will be gone. So in order to get the stress to go all the way down to deep structures, you have to obviously use a larger and larger compressor. You may reach a point where the compressor is so large that the footprint is too big on the body, and for practical considerations that may be bad. So the reason small parts are mentioned is that we can get away with standard, for example, 40 mm type transducers. And as you have seen from these images, you still have plenty of stress to work with. But it does decay, as you've seen in some of the other things. And it's really a matter of how small a stress can we measure over the noise to get to the depth we want. So it's a sensitivity issue. And you know, up there in your sensitivity you can either up your TVG up to a point, or you can hit the transducer with more power. So in our case, you can either get better cross-correlation functions, or we can make a larger compressor, which is akin to increasing the power. Those two things will increase the penetration.

THUSSEN: I'll make one more comment. As far as you've explained now, it's still more or less a matter of scaling, like you do with ultrasound in general. If you have a small organ, you use a small transducer at a high frequency. You have to keep the organ at a small size, or you could work with a lower frequency and have a larger transducer. So I think that if you talk about penetration of 5 cm for breast, you could talk about 15 cm in liver with a lower frequency. So there's no fundamental problem.

OPHIR: There's no fundamental problem, yes.

HILL: So far, your interest and other people's interest has been in applying this in tumors, but I wonder whether there are not other applications and if you've thought about them. Maybe you would have to use some of these applications using internal stimulus rather than external stimulus, but how about myocardial infarction? Is that a pathology that's likely to lead to changes in elastic properties of tissue? And would you be able to detect that, do you think?

OPHIR: I don't profess to be an expert on myocardium. I think Professor Miller has worked in this area for many years and in fact has told me and others too that he's been working on some stiffness matrices for muscles and so on. So perhaps you can bail me out.

Miller: Well, there are many other experts in the audience who could say much more wisely than I could, but certainly to the touch, scar from mature infarct is very, very stiff compared to normal myocardium. And there are true experts here who could say more. So it's a very good candidate. And yes, as Jonathan alludes to, we have a very serious program to map out the elastic stiffness coefficients for heart under normal conditions and under a variety of pathologies. And I won't have time in my talk later on today to present this, but we are systematically measuring the five elastic stiffness coefficients required to characterize the uniaxial structure of a thin layer of heart, and from that we can generalize to thick layers which have rotations of those elementary layers. And we have already published C11 and C33. We're about to submit to Professor Dunn and Journal of the Acoustical Society of America C13. So I hope if someone in this room refers it, they'll give it favorable reviews. It's just about to be mailed. We'll do that when I get home. And C44 and C66 are very close. So that's where things stand.

TANAKA: It was indeed a very stimulating and interesting presentation, particularly for the cardiologists. Elasticity is related to arteriosclerosis and other disturbances, and therefore this is a very crucial issue. I have two questions. One is related to this elasticity. There is this structural dependent elasticity and material dependent elasticity. I think there are two types: elasticity of structure and material. With what you have told us, how can you sort of discriminate between the two, or do you take the two as a whole? Could you enlighten us on this aspect?

OPHIR: The question from Dr. Tanaka states that there are at least two, probably two, kinds of elasticity. One is related to the material itself, and the other to the structure of the material. I'm glad you asked that question, because I think that in the morning, for example, some people described bulk modulus of elasticity and how this relates to the formulas that have to do with the speed of sound or ultrasound in the body. Maybe I can try to describe it in terms of a simple example. If you have a rod of steel, if you put an ultrasonic pulse on one end, it goes through and comes to the other side after several microseconds. The speed has to do with the fact that it is steel, pretty much. Now if you take that same rod of steel and you coil it up into a spring, now you can sit on it and bounce on it and it has a different elastic constant all together. You can still pretty much take the same ultrasonic pulse and propagate it through that coiled steel, and it will exhibit pretty much the same speed of ultrasound, but you will now have a kind of low-frequency structural component, or macro structural component, which has to do with the fact that this same steel bar which still has the same ultrasonic speed of sound has a new elastic modulus, which was acquired due to the shape and the form into which it was put. There is some literature out there that suggests that the type of elasticity that we're talking about here, which is a low-frequency type of elasticity really has to do with the macro structure of the tissue. So it doesn't have much to do with the molecules and the atoms and their elastic interactions, but rather the larger structure, which has to do with the tissue composition itself.

QUESTION: You have shown us a very beautiful picture of an elastogram of a tumor. For taking that picture, how long does it take for a particular patient, or tumor, say?
OPHIR: I can tell you that right now, it takes a long time. Because the system that I showed is very cumbersome, it is basically a research tool. So it has not been optimized in any way at all. The fundamentals, though, are such that we should be able to move the transducer, take one image in about one-thirtieth of a second, move the transducer in another thirtieth of a second and take the second image in the same amount of time. So maybe in a tenth of a second, we should be able to get the two ultrasound images that we need. Right now, as I mentioned, it takes two or three minutes to process on a personal computer with an array processor, but we have already looked at some ways to compute one bit cross-correlation functions, which can be done much faster and basically still contain the phase information to the point where we can see very little difference between an eight-bit correlation function, or an eight-bit rf, and a one-bit rf for this purpose. So I think ultimately it should be possible to get a frame rate of maybe 10 per second or five per second or something like that.