Elastography is performed on digital signals. Time delay is not generally an integral multiple of the sampling period. Thus, correlation functions can be interpolated to improve the precision of the time delay estimates [126-128]. Elastography commonly uses a parabolic or cosine fit. It is computationally simple, but can introduce a cyclic bias error [52]. If the displacement estimates have a cyclic error, the strain, obtained by taking a gradient of the displacements, will also contain a cyclic error. The authors have determined that any non-linear operation such as the logarithmic amplitude compression greatly enhances this bias error [129]. This bias error manifests itself as horizontal bands of alternate black and white lines on the elastograms. The spatial frequency of this bias increases with increasing strain. Thus, this artefact is strain dependent. This particular artefact has been named the ‘zebra’ artefact [130]. Figure 25a illustrates the appearance of the zebra artefact. This is the elastogram of the tissue-mimicking phantom that has a hard inclusion in a homogeneous background. The elastogram has been processed with log compression of the echo signal and the correlation function has been interpolated with a parabola. The elastogram has horizontal bands of black and white going through the image. In the region of larger strains, the bands are more closely packed than in the hard inclusion where the strain is lower.

The other signal processing artefact appears when large signal overlaps are used, which produce correlated noise patterns. This artefact also appears as horizontal structures like the zebras. However, there are some important differences. The structures are generally much thinner (vertically) and shorter (horizontally). They do not go through the entire width of the image and are strain independent. This particular artefact has been dubbed ‘worms’. An illustration is shown in Fig. 25b.

### 11 TISSUE IMAGING RESULTS

#### 11.1 In vitro elastography

As shown in Fig. 8, for the low-modulus dynamic range, the CTE is close to 0 dB, which means that the strain contrast is nearly equivalent to the Young’s modulus contrast. This important observation was recently verified using post-mortem ovine kidneys [11]. For this study a total of 20 kidneys were used. A summary of the results is shown below.

Figure 26 shows matching sonogram, elastogram and a gross pathology photograph of an ROI from a typical ovine kidney, which was embedded in a block of clear gelatin for support during compression. As shown by the sonogram of Fig. 26, the kidney is composed of two different tissue types: the hyperechoic external layer is the renal cortex (RC) and the hypoechoic internal structures (including the renal pyramids and the calices) are known as the renal medulla and sinus (RS). Notice the acoustic shadow just below the renal pelvis. This shadow
Fig. 26  Longitudinal (a) sonogram, (b) elastogram and (c) pathology photograph of an ovine kidney in vitro. In the elastogram, black corresponds to low strain and white to high strain. This elastogram is obtained after a single (0.5 per cent) compression of the gelatin block that contained the kidney. The strains are estimated using a least-squares strain estimator [75] applied on displacement data obtained using one-dimensional cross-correlation (1.8 mm window length and 60 per cent overlap). The scan was obtained using the 5 MHz, 40 mm linear array transducer of a Diasonics Spectra II scanner. The elastogram demonstrates structures that are consistent with a stiffer renal cortex and medullary pyramids (of which at least seven are seen), softer columns of Bertin and very soft fatty areas at the base of the columns in the renal sinus. Areas of sonographic echo drop-outs outside the kidney and in the acoustically shadowed areas distal to the renal sinus are intentionally blanked in the elastogram.

is due to the high reflectivity of the overlying pelvic tissue. Note the paucity of sonographic detail in the renal medulla and sinus.

From the elastogram of Fig. 26b it can be seen that the strain gradually increases from the RC to the interior of the RS. The strain variation is better illustrated by the plot (Fig. 27a) of the strain across the short axis of the kidney at the location shown by the arrow (Fig. 26b). This strain variation suggests that the modulus of the kidney tissue gradually decreases from the RC to the RS. This observation was indeed verified using independent measurements of Young’s moduli using an Instron testing machine (Fig. 27b). The presence of several stiff, conical areas can also be seen inside the

Fig. 27  (a) Strain profile taken from the elastograms of Fig. 26a along the short axis of the kidney at a depth shown by the arrow in Fig. 26b. (b) Modulus contrast measured using the Instron machine (———) compared to the strain contrast measured using elastograms (—–). The Instron and elastographic results were obtained from eight different kidneys. Observe that the modulus contrast variation in the kidney is similar within the error bars to the strain contrast variation. The error bars represent standard deviations.
medulla, which are separated by columns. These are consistent with the appearance of the medullary pyramids and the columns of Bertin [131].

As shown by Fig. 27b, the strain contrast is essentially equivalent to the modulus contrast. This experimental result is corroborated theoretically using a model of the contrast transfer efficiency (CTE). Indeed, as shown by Fig. 8, for a modulus dynamic range of less than $\pm 3 \, \text{dB}$, the average efficiency is about $-1.46 \, \text{dB}$, which also means that the strain contrast is only about 10 per cent less than the equivalent Young’s modulus contrast. Therefore, at low contrasts, after controlling the external boundary conditions (compressor size), the elastogram may be interpreted as a quantitative approximation of the inverse of the relative Young’s modulus distribution in the tissue. This is an important result that should allow the imaging of actual relative modulus distributions in normal tissues and within various pathological lesions such as tumours, as long as the modulus contrast within these tissues is low ($\leq 6 \, \text{dB}$). In such cases, elastic modulus reconstruction may not be necessary.

An example of the visualization of the canine prostate gland is given in Fig. 28. It is evident that the elastographic appearance of the prostate is quite different from that of the sonographic appearance.

11.2 In vivo elastography

Because the case with which compression can be applied to the breast, it is an ideal organ on which to perform elastography. Also, the relative stiffness of breast cancers, as compared to benign fibroadenomas and cysts, makes a method such as elastography which estimates tissue stiffness an attractive tool for distinguishing benign from malignant lesions. For these reasons, virtually all in vivo elastography work to date has been performed upon breast lesions [10].

Initially, the procedure was performed on women with suspicious lesions detected mammographically. The woman was examined in the upright position with the breast placed upon the imaging table of a mammography machine. The transducer was attached to a computer-controlled stepper motor, which replaced the compression paddle of the mammography system, and compression was applied downwards on the breast. This had the advantage of providing a stable platform against which to compress the breast. It also allowed elastographic evaluation of non-palpable lesions visible only on mammography, by using a cut-out grid compression paddle with the ultrasound transducer/stepper motor being positioned in the cut-out at the coordinates of the lesion seen on a cranial caudal mammogram.

Between 1993 and 1996, a total of 50 breast lesions were studied just prior to surgical biopsy with this approach using a Diasonics Spectra real-time scanner fitted with a 5 MHz linear array transducer. Radiofrequency data (digitized at 48 MHz) acquired before compression were windowed into 3–6 mm segments and were cross-correlated with similarly windowed data obtained after a 0.3–0.6 mm compression. Up to six elastograms were generated per lesion.

The elastogram is typically displayed side by side with a B-mode sonogram generated from the same RF data. This type of display greatly facilitates identification of lesions on elastography and makes lesion characterization much simpler. Using an elastographic display in which harder tissues are displayed as darker shades of grey, the elastogram often resembles the appearance of an inverse B-mode image. Fatty breast tissue that is dark on the sonogram appears bright (soft) on the elastogram and bright fibroglandular tissue on the sonogram.

![Fig. 28 Matching (a) sonogram, (b) elastogram and (c) gross pathology photograph of an anterior–posterior transverse cross-section of a canine prostate gland in vitro. The prostate was obtained immediately after removal and cast in a block of echo-free gelatin. Imaging was done at room temperature with a Diasonics Spectra clinical scanner that had been modified for elastographic imaging, using a 5 MHz, 40 mm array transducer. The field of view is approximately 40 × 40 mm². The elastogram demonstrates anteriorly the isthmus as a low strain area, centrally the verumontanum as a small, dark (hard) circular area just below the lumen of the urethra, which is depicted as an inverted V-shaped soft area. Observe the thin bright lines converging towards the urethra, which are consistent with the prostatic ducts shown on the pathology image.](image-url)
appears darker (stiffer) on the elastogram. Benign fibroadenomas may appear stiffer (darker) than surrounding tissue on elastograms, but often are the same stiffness or softer (brighter) than the surrounding tissue (6 of 15 in the present series). Fibroadenomas generally have smooth regular borders on elastography and their measured size on elastograms was almost always the same or smaller than their diameter on sonography.

Of the 12 cancers that were studied in the initial series, all but one were visible. Most cancers had a stiffer (darker) appearance (Fig. 29) than fibroadenomas but there was considerable overlap in this feature. Cancers often had a mixed appearance with both stiffer and softer areas being present. The transverse diameter of cancers, however, was generally larger on elastograms than on sonograms in all but two cases. This is probably due to the firm desmoplastic reaction surrounding cancers being included as part of the lesion measurement on elastography. Using the combination of lesion stiffness and the difference between the sonographic and elastographic lesion diameters, it was possible to distinguish 8 of 11 fibroadenomas from cancers. This suggests that a significant reduction in biopsies of benign lesions is possible using elastography and sonography together. Also, elastography was found to be useful in the characterization of areas of shadowing on sonograms. Areas of shadowing caused by cancer demonstrated a discrete mass on the elastogram, whereas areas of shadowing caused by poor transducer contact, overlying refraction or mild fibrosis showed no abnormality on the elastogram.

Performing elastography in the upright position led to several problems. The patients were often unable to hold motionless for the time needed to acquire data resulting in useless elastograms. A much more severe problem was the fact that only about 40 per cent of the breast masses were too far away from the chest wall for the ultrasound transducer to access the lesion. In the others, the bulkiness of the transducer and surrounding pressure plate (when held in the vertical position) prevented the ultrasound beam from reaching the lesion. Because of this problem, the next step was to try performing elastography in the supine or oblique supine position, as is done for normal breast sonography. In this situation, the transducer cannot press the breast tissue against a flat surface and the chest wall itself must serve as the base. Since the chest wall has an undulating surface composed of ribs and muscle layers, there was potential for artefacts to be created in the elastogram. The present studies so far have shown this not to be a problem. The supine positioning allows access to all breast lesions and opens the door for a clinically useful elastography instrument.

Noise in elastograms was a significant problem in the first clinical study. This noise was suppressed using five-point median filtration on the final images which reduced the noise but decreased the spatial resolution of the images. To further reduce the noise, the authors have begun to acquire data using multiple compressions. Between three and six compressions are used and the strain data from all pairs of images in the data set are used to generate the final elastogram. An example of a cancer using four compressions is shown in Fig. 30. Further enhancements such as signal stretching should further reduce the noise and allow images to be generated with less noise and higher spatial resolution.

12 SUMMARY AND CONCLUSIONS

The early hypothesis underlying the efforts to measure and image the elastic modulus of tissues has been that

Fig. 29 (a) Sonogram and (b) elastogram of an invasive ductal carcinoma in vivo at 5 MHz. Note the irregular mass seen on the elastogram where only an echogenic band and shadow are seen on the sonogram. The lesion is clearly visible as a dark (hard) area on the elastogram, and elastographic structures are visible in the distal sonographic shadows. The elastographic scan size is approximately 40 × 40 mm².
soft tissue modulus contrast exists, especially between normal and abnormal tissues. Indeed, it has been shown recently that two important and rather arbitrary tissue contrast domains exist. The first is the existence of a large (>20 dB) modulus contrast between normal and some pathological tissues (at least in the breast) [50] and the second is the existence of low (<6 dB) to moderate (<20 dB) modulus contrast among various normal tissues in the kidney and breast [11, 50]. It has also been shown that procedures such as tissue ablation have a profound effect on tissue elastic moduli [110]. As shown in this article, these observations, together with some initial clinical observations showing the ability of elastography to detect and characterize sonographically occult breast cancers [10], are providing the catalyst for continuing the vigorous development and application of elastographic methods to medical imaging problems.

The estimation and imaging of tissue strains is by definition a three-dimensional problem. When the tissue is compressed, the near incompressibility of most soft tissues means that strain tensor components are generated in all directions simultaneously. Until recently, workers in the field had assumed that single-view ultrasonic methods could not be used for precision lateral displacement and strain estimates [58, 59, 132]. As a result, they are essentially limited to displacement and strain estimations in the axial direction only. Lubinski et al. [59] suggested using the precision axial displacements to compute the lateral displacements under a set of assumptions about boundary conditions and incompressibility of the tissue. Konofagou and Ophir [42] have demonstrated that it is in fact possible to make precision estimations of lateral displacements and produce images of lateral strain and Poisson’s ratio distributions in tissues, if proper overlap between adjacent ultrasonic beams is maintained. With 1.5-dimensional arrays, or by using a one-dimensional array and measuring the residual eleva-

Fig. 30  (a) Sonogram and (b) elastogram (average of four compressions) of invasive ductal carcinoma in vivo (noisy areas on the left side and at the bottom of the elastogram have been blacked out). Note the larger size of the lesion in the transverse dimension on the elastogram (crosses). The darkest (hardest) regions of the tumour correspond to the bright foci on the sonogram, which represent microcalcifications. The image size is approximately 40 × 40 mm².

tional decorrelation after correcting for the other two components, it should be possible to precisely estimate all three longitudinal components of the strain tensor in tissues using clinical array scanners. Poisson elastograms may be important in the imaging of poroelastic, oedematous and other tissues.

Given the existence of significant modulus contrast in many normal and abnormal tissues and the ability to estimate some of the components of the strain tensor, the noise performance of these estimations becomes the important parameter that dictates the achievable image quality with which tissue elastograms can be made. The strain filter framework [43] has been developed to describe the trade-offs among all the technical parameters of the ultrasound instrumentation in terms of their influence on the elastographic image parameters. Using this formalism, it has been demonstrated [43] that axial elastograms with a high SNR, wide strain dynamic range [124, 125] and good strain sensitivity can be achieved at millimetre resolutions. These can be further improved by correcting for lateral displacements [42, 60, 61]. Given, further, that axial or lateral elastograms display the distributions of the respective strains and not of the moduli, a contrast transfer efficiency (CTE) metric has been defined and calculated [45, 46], which adds a description based on elasticity theory of the efficiency with which actual modulus contrast is converted to elastographic strain contrast under known conditions. It has been shown [11] that for low-contrast situations, such as in the normal ovine kidney, the strain image is a reasonable representation of the actual modulus image. For high-contrast situations, inverse problem treatment may be necessary in order to minimize artefacts, as long as there is reasonable knowledge of the boundary conditions. It has also been shown that elastography holds promise in the evaluation of breast masses in vivo [10]. Based on the progress described in this article, it is accu-
rate to say that at this point the fundamental aspects of elastographic imaging are reasonably well understood and can be theoretically predicted and practically analysed.

Many interesting challenges remain in the development of this new field. In principle, it should be possible to generate elastograms in real-time, perhaps by reducing the cross-correlation computations to 1-bit hardware operations, which have been shown to be effective [25], or by using fast digital signal processing (DSP) chips. The ultimate limitation on speed is the speed of sound and the speed of propagation of the elastic wave in tissue. The current need for a transducer-holding apparatus is another major limitation. This could be overcome by estimating the unpredictable coarse and fine lateral and elevational displacements [42, 61] encountered in hand-held elastography [72] and correcting the axial elastogram appropriately so that quality images can be generated. This approach is powerful in that it is able to remove severe decorrelation noise that is introduced when the local strain filter at any point in the image enters the Barankin bound due to excessive and/or undesired motion [99]. Another solution may involve the use of incoherent strain estimators that are less sensitive to jitter and other undesired motions. A ‘stressmeter’ in the form of an elastic layer attached to the transducer or the target [24] may be used in conjunction with a hand-held device to allow automatic non-stationary image calibration for uneven compressions. The optimal elastographic protocols that are to be followed when imaging certain tissues are as yet unknown. These include the amount of pre-compression, the applied imaging compression, the number of sonographic frames and the (adaptive) algorithm(s) to be used for image optimization, and the relationship of these protocols to the specific elastic properties (such as contrast and nonlinear stress–strain behaviour) of most tissues. While elastographic artefacts are fairly well understood [25], their possibly ambiguous role as detractors or facilitators of lesion detection and/or diagnosis remains unknown. The role of the inverse problem treatment of elastograms [56, 57, 108] and the related definition of tissue moduli at different scales and under variable boundary conditions remains obscure. In principle, these methods could be valuable for reduction of artefacts and for quantization of elastograms as shown, but major fundamental issues relating to their applicability under various known or unknown boundary conditions must first be resolved. Related techniques, such as high-frequency, high-resolution methods [34, 35] applied intravascularly, may also develop as useful adjuncts to the current sono-

graphic methods. Another important area that could greatly benefit from the incorporation of elastographic techniques is the area of thermal or cryogenic tissue ablation monitoring. It is known that standard sono-

graphic techniques are not well suited for monitoring such procedures due to low contrast. The authors have recently shown that elastography offers high precision in monitoring laser and high-intensity focused ultrasound (HIFU) applications [110, 133]. The area of elastographic phantom development is another important area that will require attention, since these must be used to objectively test all new developments. Parker et al. [48], Hall et al. [134] and DeKorte et al. [34] have described promising methods for independently manipulating the sonographic and elastographic properties of gelatins to achieve a reasonable range of elastic moduli.

In conclusion, the authors believe that while elastography has progressed rapidly in the past several years, much progress has yet to be made in order for it to become a viable clinical and investigational tool. Even at this early stage, however, it is evident that there exists a fortunate set of favourable biological, mechanical and acoustical circumstances that, when combined, are likely to allow the attainment of this goal.

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