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REVIEW

Ultrasound imaging

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Abstract

Ultrasound imaging is now in very widespread clinical use. The most important underpinning technologies include transducers, beam forming, pulse compression, tissue harmonic imaging, contrast agents, techniques for measuring blood flow and tissue motion, and three-dimensional imaging. Specialized and emerging technologies include tissue characterization and image segmentation, microscanning and intravascular scanning, elasticity imaging, reflex transmission imaging, computed tomography, Doppler tomography, photoacoustics and thermoacoustics. Phantoms and quality assurance are necessary to maintain imaging performance. Contemporary ultrasonic imaging procedures seem to be safe but studies of bioeffects are continuing. It is concluded that advances in ultrasonic imaging have primarily been pushed by the application of physics and innovations in engineering, rather than being pulled by the identification of specific clinical objectives in need of scientific solutions. Moreover, the opportunities for innovation to continue into the future are both challenging and exciting.

1. Introduction

A review of the state of the art of ultrasonics in medicine and biology was published in *Physics in Medicine and Biology* about 30 years ago (Wells 1977). At that time, the propagation of ultrasound in tissue was considered to be linear, there was a reasonable grasp of the processes of attenuation and scattering, and real-time imaging was a possibility, particularly with the then recent introduction of electronically controlled transducer arrays. Blood flow was being measured using the ultrasonic Doppler effect. The foundations of the understanding of ultrasonic bioeffects were in place but the safety of ultrasonic imaging was a controversial issue.

The next 20 years were a period of considerable activity. By about 7 years ago (Wells 1999), the significance of nonlinear propagation and tissue inhomogeneity had been recognized. Improved piezoelectric transducer materials had become available and real-time

transducer arrays had largely replaced other scanning techniques in clinical practice. The importance of image speckle had been appreciated, leading to a better understanding of the scattering of ultrasound, particularly by blood. Colour flow imaging was commonplace. Three-dimensional imaging was becoming clinically relevant with the development of more powerful computers. Specialized imaging methods, including endoluminal scanning, synthetic aperture imaging, computed tomography, elasticity imaging, microscanning, contrast agents and tissue harmonic imaging, were beginning to emerge.

Ultrasonic imaging is now a mature technology, to the extent that it has a well-established place in clinical practice, as confirmed by the fact that it currently accounts for about one in four of all imaging procedures worldwide. This does not mean, however, that the pace of development, either of the understanding of the physics of the interactions between ultrasound and tissue or of innovation in techniques and instrumentation, has slowed down. Indeed, the opposite is true. In this review, an attempt is made briefly to describe most of the significant advances that have taken place in the last 10 years, from the perspective of the physics and, to some extent, the engineering involved. Because the subject is vast and the space available is limited, the review takes the form of a series of short vignettes, each of which ends with a list of representative publications to which the reader interested in pursuing the topic may find it helpful to refer. Even so, significant topics have idiosyncratically had to be omitted. Also, there is no space for figures to illustrate all the principles involved and it would obviously be inappropriate to make a random, sparse selection. Nevertheless, to whet the appetite of the reader, figure 1 presents three ultrasonic images, two contemporary and one from about 25 years ago, to illustrate something of the progress which has been made in the quality and clinical usefulness of ultrasonic scanning over the last quarter of a century.

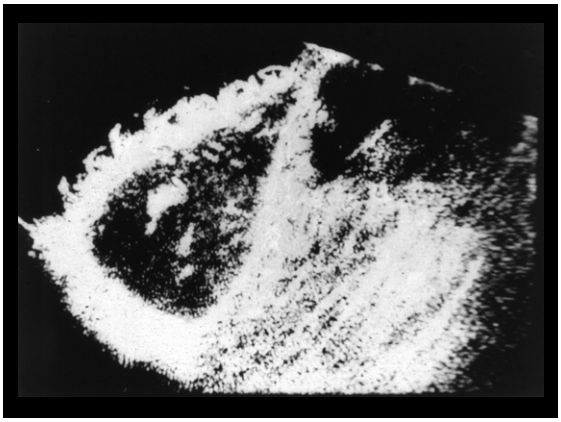
2. Mainstream technologies

In this section, the state of the art in the mainstream technologies which underpin the contemporary clinical applications of ultrasonic imaging is reviewed. The range of these technologies is now so great that it has been necessary to be selective in choosing those technologies which seem to be most important; it is hoped that this selection will not be thought to be too biased.

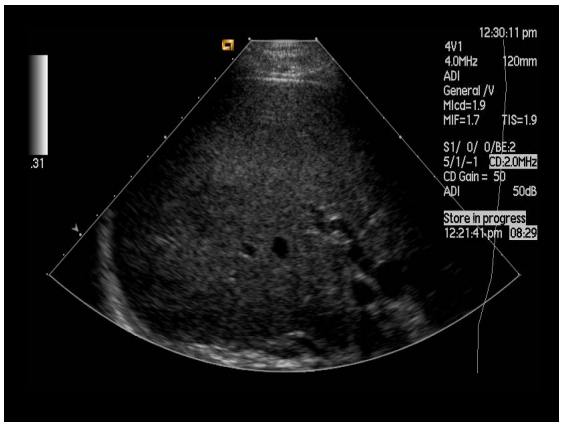
2.1. Transducers

In some respects, the transducer is the most critical component in any ultrasonic imaging system. In other words, such is the state of the art in systems such as electronic circuitry and display technology that it is the performance of the transducer which determines how closely the limits imposed by the characteristics of the tissues themselves can be approached.

Nowadays, the transducers which are in clinical use almost exclusively use a piezoelectric material, of which the artificial ferroelectric ceramic, lead zirconate titanate (PZT), is the most common. The ideal transducer for ultrasonic imaging would have a characteristic acoustic impedance perfectly matched to that of the (human) body, have high efficiency as a transmitter and high sensitivity as a receiver, a wide dynamic range and a wide frequency response for pulse operation. PZT has a much higher characteristic impedance than that of water but it can be made to perform quite well by the judicious use of matching layers consisting of materials with intermediate characteristic impedances. Even better performance can be obtained by embedding small particles or shaped structures of PZT in a plastic to form a composite material: this has a lower characteristic impedance than that of PZT alone, although it has similar ferroelectric properties.



(a)



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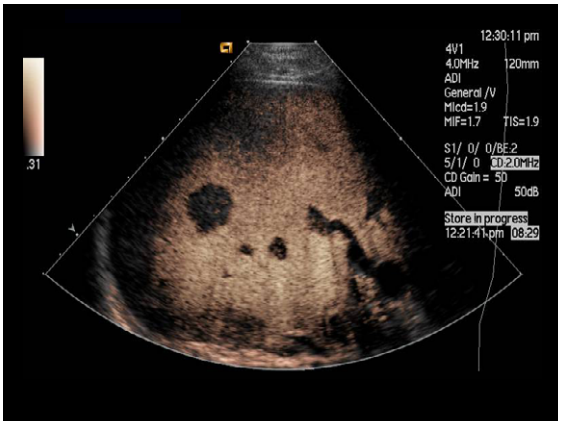

(c)

Figure 1. Ultrasonic liver scans, illustrating the improvement in quality which has occurred over the last 25 years. The images are (a) a scan which was considered to be of high quality in the early 1970s and which would have been interpreted as supporting the diagnosis of multiple metastases, (b) a scan made with a modern system, in which a metastasis can just be perceived towards the right side of the patient (i.e., towards the left of the image) and (c) a scan of the same patient, in which this lesion is clearly apparent following the administration of an ultrasonic contrast agent.

Polyvinylidene difluoride (PVDF) is a plastic which can be polarized so that it has piezoelectric properties. The piezoelectric effect can be enhanced by the addition of small quantities of appropriate chemicals. The advantages of this material are that it has a relatively low characteristic impedance and broad frequency bandwidth; it is fairly sensitive as a receiver but rather inefficient as a transmitter.

Piezoelectric transducers are normally operated over a band of frequencies centred at their resonant frequency. The resonant frequency of a transducer occurs when it is half a wavelength in thickness. Typically, a PZT transducer resonant at a frequency of, say, 3 MHz is about 650 μm thick and this means that it is sufficiently mechanically robust for simple, even manual, fabrication techniques to be employed in probe construction. Higher frequency transducers are proportionally thinner and, consequently, more fragile.

The potential of capacitive micromachined ultrasonic transducers (cMUTs) at least partially to replace PZT and PVDF devices in ultrasonic imaging is the subject of current research. A cMUT consists of a micromachined capacitor, typically mounted on a silicon substrate and with a thin electroded membrane as the other plate of the capacitor: this acts as the active surface of the transducer. A dc voltage is applied between the plates of the device; the application of an ac voltage causes the membrane to transmit a corresponding oscillatory force, while a received wave causes a corresponding change in the spacing between the plates, thus generating an electrical signal. cMUTs are adequately sensitive as receivers, but need high voltages to be effective transmitters. Some of the potential advantages of these devices are that they can be fabricated into arrays with integrated electronics and, if manufactured in large quantities, could be relatively inexpensive.

Although some simple probes contain single-element transducers (e.g., one element for transmitting and one for receiving, in a continuous-wave Doppler system), most modern imaging systems use arrays of transducer elements for beam forming (see section 2.2).

For further information, refer to Davidsen and Smith (1998), Foster *et al* (2000), Hunt *et al* (1983), Jin *et al* (1998) and Seyed-Boloforosh (1996).

2.2. Beam forming

In ultrasonic imaging, the beam may be scanned through the tissue either by mechanical movement of a single element or an annular array transducer, or by electronic control of a transducer array consisting of a number of small elements. For two-dimensional scanning, the array typically consists of 256 elements. The simplest arrangement is a linear array, within which an aperture is formed from, say, 16 contiguous elements and which is stepped along the array element by element to acquire an image with, in this example, 241 lines. The same number of lines in a sector format can be acquired by curving the array into a segment of a cylinder. A sector scan can also be acquired by controlling the phases of the signals associated with each of the elements in the aperture. Whatever the arrangement, the application of distinct time delays to excite each element focuses the transmitted beam at a particular range. By transmitting several beams in the same position but with different foci, a sharply focused transmitted beam can be synthesized. On reception, the focus can be swept along the beam by dynamically changing the time delays associated with the active transducer elements, so that its position coincides continuously with that of the instantaneous origin of the echoes. Both when transmitting and receiving, the amplitudes of the signals associated with the active elements can be weighted to minimize the amplitudes of the beam side lobes, which are critical in determining the image contrast resolution. Also, the number of elements in the active aperture can be dynamically increased with increasing depth of penetration to

maintain a constant *f*-number, within the limit imposed by the total length of the array and optimized to minimize the effect of tissue inhomogeneity.

For three-dimensional imaging, the two-dimensional scan plane produced by a one-dimensional linear, curved or phased array can be swept mechanically, either linearly in the orthogonal direction or through a sector. Recently, two-dimensional transducer arrays have been developed. Because of the very large number of transducer elements in these arrays, beam forming in three dimensions can be achieved more economically but with some degradation in performance by sparsely populating the array. For real-time three-dimensional scanning, several transmitting beams can be synthesized simultaneously; a single receiving beam can be associated with each transmitting beam, or, by increasing the width of each transmitting beam, several sharply focused receiving beams can be accommodated simultaneously in each transmitted beam.

The beam-forming time delays and aperture apodization functions are digitally controlled. The sampling frequency has to be at least twice the highest ultrasonic frequency, in order to avoid aliasing. Further improvement can be obtained by applying a finite impulse response digital filter or by demodulating the radio-frequency signals to baseband to obtain quadrature signals so that the associated time delays can be finely adjusted by phase rotation.

A very powerful software tool, Field II, has been developed to simulate ultrasonic beam and image formation. The current program assumes linear acoustics and it is freely available under certain restrictions.

An intriguing development in high-speed imaging has recently been brought about by the application of limited diffraction beams. A limited diffraction beam can be produced by appropriate excitation of a transducer array. Following the transmission of a single plane wave pulse, the received signals are weighted with limited diffraction beams simultaneously to produce multiple A-lines which can be used to create a complete two-dimensional image.

For further information, refer to Brown and Lockwood (2005), Jensen (2002), Li and Huang (2002), Lu (1998) and Ranagathan and Walker (2003a, 2003b).

2.3. Pulse compression

Ultrasonic pulse-echo imaging traditionally involves the transmission of as brief a pulse of ultrasound as is consistent with the frequency of ultrasound determined by the required penetration into the tissue. Considerations of the safety of such brief high-powered pulses, the nonlinear properties of tissue and the destruction of contrast agent microbubbles reveal that this approach may often not be optimal. Coded transmission pulses have the potential to increase the penetration depth, to improve the signal-to-noise ratio and/or to increase the image frame rate. The principle is simple. The transmitted pulse has a relatively long duration and low amplitude, in comparison with the traditional brief pulse, and the frequency of the pulse typically is either swept so that it is a chirp, or it is modulated with, for example, a binary code. The signals received as echoes from within the tissues are then correlated with a signal corresponding to that which was transmitted, by means of a matched filter. This has the effect of compressing the received signals so that they correspond to a traditional pulse-echo wavetrain, which can be further processed to provide the image information.

Pulse compression schemes of this kind have long been used in radar, sonar and mobile communications systems. The situation in ultrasonic imaging, however, is rather more challenging. In radar and sonar, the purpose is usually to detect isolated targets, whereas, in ultrasonic imaging, virtually the whole of the tissue is occupied by reflectors and scatterers. In ultrasonic imaging, there is strong frequency-dependent attenuation, which is much less of a problem in radar and sonar. Added to this, the bandwidth of ultrasonic transducers is limited.

Finally, ultrasonic echoes tend to be dominated by speckle, whereas the echoes in radar and sonar are much less spatially variable. The effects of these processes on pulse compression schemes for ultrasonic imaging are to introduce echo range ambiguities resulting from the temporal side lobes which are produced in the cross-correlation process.

System optimization with a transducer array operating with coded pulses also needs to take into account the ultrasonic beam axial side lobes. In comparison with traditional brief pulse transmission, however, current pulse compression techniques can result in a signal-to-noise ratio improvement approaching 20 dB, with temporal side lobes of below 60 dB, and the image frame rate limitation imposed by cross-talk between spatially separated beams simultaneously acquiring image information can be reduced by up to a factor of as much as 25.

For further information, refer to Misaridis and Jensen (2005a, 2005b, 2005c).

2.4. Tissue harmonic imaging

It was noted, perhaps by accident during experiments with ultrasonic contrast agents (see section 2.5), that the echoes from deeper parts of tissues being imaged by pulse-echo techniques actually contain quite significant components at the second harmonic of the transmitted frequency. These harmonic components arise because a finite-amplitude transmitted pulse is distorted in its propagation through inherently nonlinear tissue. Moreover, by selecting the second harmonic frequency signals for imaging in the absence of contrast agents, improvements in spatial resolution and other aspects of the image were apparent, particularly when examining 'technically difficult' patients, such as those with obesity and/or dense muscle structure. The reasons for this are that, because the harmonics develop slowly, the low-frequency transmitted beam suffers relatively little distortion in passing through the superficial tissues, most of the second harmonics develop in the main beam rather than in the lower amplitude side lobes and the side lobes of the transmitting and the receiving beams have different angular distributions, whereas the main beams are coincident.

Although tissue harmonic imaging at the second harmonic frequency is apparently better than imaging at the fundamental frequency, there is some controversy over what aspects of the imaging are 'better' and the process certainly has some difficulties. Thus, the bandwidth of the transducer necessarily has to accommodate the frequency spectra of both the transmitting and receiving beams, and so it is inevitable that some of the high-frequency components of the spectrum of the short transmitted pulse leak into the spectrum of the received signals. Also, the useful dynamic range of the received signals is reduced, because their absolute amplitude is closer to that of the system noise.

An improvement in tissue harmonic imaging can be obtained, at the expense of image frame rate, by transmitting pulses with sequentially reversed polarities and adding consecutively received echo wavetrains. This pulse inversion technique effectively removes signals with odd harmonic frequencies (including echoes at the fundamental transmitted frequency) and doubles the amplitudes of those at the second harmonic and higher even frequencies.

Of course, harmonics higher than the second one are also produced as a result of the nonlinear propagation of the transmitted pulse. Although they are relatively weak, a usable signal can be obtained by summing the third, fourth and even the fifth harmonics to constitute what has been called the superharmonic component of the received echoes. For this, a composite broadband transducer is required. Superharmonic imaging is characterized by high spatial and temporal resolutions and the relative absence of clutter.

For further information, refer to Bouakaz and de Jong (2003), Browne *et al* (2005), Ma *et al* (2005) and Tranquart *et al* (1999).

2.5. Contrast agents

Although the echo-enhancing property of small gas-filled bubbles suspended in blood had been known for some 25 years, it was not until the 1990s that the production of encapsulated microbubbles began to be standardized and their behaviour in ultrasonic beams propagating in free liquids, blood and solid tissues began to be studied seriously.

Typically, an ultrasonic contrast agent microbubble contains air or a high-molecular-weight low-solubility gas encapsulated in a lipid or albumin shell. The bubble may have a diameter in the range 1–10 μm, so that, when suspended in blood, it is small enough to pass through the capillaries. Perhaps more important than this, however, is the fact that, although the diameter of the bubble is smaller by a factor of perhaps 1000 than the wavelength of the ultrasound, it can be made to resonate at the ultrasonic frequency. The resonant frequency of the bubble increases as its diameter decreases if the shell properties are unaltered. When introduced even at high dilutions into blood, the echoes from the blood in which microbubbles are suspended are greatly enhanced, particularly when they resonate at the ultrasonic frequency. This is because of their intrinsic compressibility, which is about 20 000 times greater than that of water. This in itself provides the potential to obtain additional clinical information by ultrasonic scanning. Soon after clinical experiments with contrast agents began, however, it was noted that quite strong echo signals were also received from microbubbles at the second harmonic of the ultrasonic irradiating frequency. Because the tissues and blood itself behave in a much more linear fashion, the echoes from all the scatterers except the microbubbles can be suppressed by arranging to receive only signals in the spectrum centred at twice the transmitted frequency. By this means, it becomes possible to image small blood vessels, including the microvasculature, which contain microbubbles at so high a dilution that they are indistinguishable from the surrounding tissue with traditional pulse-echo imaging.

An important characteristic of most microbubble ultrasonic contrast agents is that they are destroyed if exposed to ultrasound of sufficient intensity. Fragmentation occurs when the bubble experiences a large expansion and subsequent contraction: the process is rapid, typically occurring on a time scale of microseconds. Thus, the microbubble population in a selected volume of tissue can be largely destroyed by the application of a brief pulse of ultrasound with a peak negative pressure typically of 2–3 MPa. This allows the time course of the subsequent refill dynamics to be observed and this is related to the perfusion of the tissue by blood. It also results in signal decorrelation, which appears as a transient disturbance on Doppler colour flow imaging (see section 2.6). There are two other significant mechanisms of microbubble destruction. Ultrasonically enhanced diffusion can destroy microbubbles in as short a time as 50 ms, depending on the properties of the shell and the gas. In the absence of ultrasound, static diffusion typically results in bubble destruction in time scales of minutes or even hours.

Second harmonic imaging with contrast agents involves a compromise between image contrast and spatial resolutions. This is because unavoidable overlap between the frequency spectrum of the transmitted beam and the passband of the receiver means that some of the transmitted power contaminates the received second harmonic signals. The problem can be solved, however, by transmitting sequentially inverted pulses and summing the resultant consecutive echo wavetrains. The linear echoes from tissues and blood sum to zero, whereas the nonlinear echoes reinforce each other. This process of pulse inversion is now commonly used significantly to enhance the sensitivity of Doppler colour flow imaging with microbubble contrast agents.

Although the ultrasonic contrast agents which are currently in clinical use are generally those based on microbubbles, there is renewed interest in nongaseous agents. Thus,

perfluorocarbon nanoparticles and gold-bound colloid microtubules seem to be quite promising, particularly as they may be immunologically targeted to specific anatomical or pathological sites. Antibodies can be conjugated with the microtubules and can provide echo enhancement which approaches that of microbubbles.

The clinical potential of targeted ultrasonic contrast agents is considerable, both for diagnosis and for drug and gene delivery. Eventually, they might even allow ultrasound to replace much of contemporary and future radionuclide imaging for functional studies, thus avoiding the problems associated with radioactivity, and with relatively high spatial and temporal resolutions.

For further information, refer to Bekeredian *et al* (2002), Chomas *et al* (2001), Hope Simpson *et al* (1999, 2001), Hu *et al* (2004), Hughes *et al* (2003), Kvikliene *et al* (2004) and Stride and Saffari (2004).

2.6. Flow and motion

Historically, the earliest ultrasonic studies of physiological motion were made using the pulse-echo technique in M-mode echocardiography. Subsequently, emphasis has largely shifted to the Doppler effect, although direct measurement of target or ensemble movement is also used, with the increase in system sensitivity, partly because it avoids the aliasing limitation inherent in the pulsed Doppler approach.

In principle, the direct measurement of the velocity profile of blood flowing in a vessel provides a more accurate basis for the estimation of the blood flow volume rate than does a single measurement of, say, the maximum blood flow velocity. There have been two approaches to the measurement of the velocity profile. First, a multigated (or infinite gate) pulsed Doppler system has been used. Second, the motion of the speckle, observed by pulse-echo ultrasound to arise from the blood, is tracked over a sequence of consecutive pulse-echo wavetrains. (It is interesting to note that it is the motion of this same speckle that actually enables the pulsed Doppler approach to result in a usable signal.) Having obtained the flow velocity profile and its variation over time (e.g., as the result of cardiac pulsation), the blood flow volume rate may be calculated by assuming the profile to be circularly symmetrical.

Colour flow imaging, which was introduced in the 1980s, similarly may be based on frequency or phase domain (i.e., Doppler) processing or on target motion tracking approaches. The early Doppler processors were simple autocorrelators, with displays colour coded either according to the mean flow velocity or to the amplitude (or power) of the Doppler-shifted signals. More recently, improved velocity estimators, such as the maximum likelihood estimator, have been introduced: they can handle a larger velocity search range which extends to lower values of velocity, and with smaller errors.

For the study of blood flow, it is the relatively low amplitude signals from the blood itself which are relevant. The magnitude of these signals can be increased by means of contrast agents and the echoes from solid tissues can be suppressed by second harmonic imaging (see section 2.4). When the greatest possible sensitivity is required (e.g., when imaging the microvasculature), the power of the Doppler signals may be used to control the brightness of the image, in distinction from colour coding the image according to the velocity of the flow.

In the study of blood flow, the accompanying motion of neighbouring solid tissues is a source of difficulty because it gives rise to relatively large amplitude Doppler signals. Various cancelling schemes are used, more or less effectively to suppress these echoes. It is usually also necessary to use a high-pass filter to remove remaining solid tissue echoes which, fortunately, move more slowly than most of the blood and so give rise to Doppler signals of lower frequencies.

Quite a long time after the introduction of colour flow imaging for the study of blood flow, it was realized that colour-coded images of moving solid tissue could also be of clinical utility. For example, some cardiac lesions are associated with abnormal motion of the myocardium. It turns out to be relatively easy to produce such images, simply by eliminating the solid tissue echo canceller and reducing the cut-off frequency of the passband filter. The process is known as tissue Doppler imaging.

For further information, refer to Bohs *et al* (1998), Dunmire *et al* (2000), Fan *et al* (2001), Jansson *et al* (2003) and Schlaikjer and Jensen (2004).

2.7. Three-dimensional imaging

Most contemporary ultrasonic scanning systems have hand-held probes which produce two-dimensional images in real time. A skilled operator moves the probe over the surface of the patient to explore the internal anatomy and thus to build up, in his or her mind's eye, a three-dimensional picture.

There are two approaches to display the scanned anatomy in three dimensions and thus, in principle, at least to some extent to deskill the process of image interpretation. First, the two-dimensional scanning probe may be moved mechanically in a predetermined trajectory or the beam may be scanned in three dimensions by means of an electrically controlled two-dimensional array so that position and orientation are directly measured and these data are used to assemble a three-dimensional image volume from the set of two-dimensional images. Second, the position and orientation of the two-dimensional scanning probe, whilst being freely moved by the operator over the surface of the patient, may be measured by sensors with respect to a frame of reference which is fixed in relation to the patient. By appropriate calibration of the spatial relationships in the system, a three-dimensional image can be assembled.

Because a three-dimensional image is assembled from a set of two-dimensional scans, scanning is proportionately slower than it is for two-dimensional imaging, unless a scheme to accelerate the process is adopted. For example, the use of separate simultaneously transmitted beams and/or the use of wide transmitted beams accommodating several narrow receiving beams is mentioned in section 2.2. As with other medical imaging modalities, the display of three-dimensional data is challenging. Since it is usually difficult automatically to segment ultrasonic images (see section 3.1), three-dimensional rendering is problematic. Currently, the easiest way to explore a three-dimensional ultrasonic image volume is usually to enable the observer rapidly to display two-dimensional images in any desired orientation within the scanned volume. Of course, this is not really ideal, especially if four-dimensional imaging (i.e., three time-varying spatial dimensions) is actually what is needed.

For further information, refer to Fenster *et al* (2001), Mercier *et al* (2005), Nelson and Pretorius (1998) and Shipley *et al* (2005).

3. Specialized and emerging technologies

In this section, some of the newer technologies which are not yet in routine clinical use are reviewed. At this stage in their development, it is inappropriate to attempt to predict which of them will prove to be the most significant. Again, the selection of which technologies are included is idiosyncratic, but they all have some elements of significant novelty.

3.1. Tissue characterization and image segmentation

Before discussing recent advances in ultrasonic tissue characterization, it is timely briefly to place the problem in its clinical context. Even histopathologists, who have specimens of the

actual tissue in question for microscopic examination, often have difficulty in making definitive diagnoses. Therefore, it seems to be highly improbable that tissues of uncertain origin and without any indication of whether they are normal or abnormal will be able to be identified from even the most complete data about their ultrasonic characteristics or from measurements of their mechanical properties derived from ultrasonic data.

In some respects, image segmentation is a simpler problem, since the objective is to delineate organs and structures and this, in principle, does not depend on actual tissue identification. Rather, it depends on the identification of characteristics which distinguish the ultrasonic data from different anatomical regions.

Diagnosticians subjectively perform qualitative tissue characterization whenever they interpret an ultrasonic scan. Attempts have been made with very many techniques to quantitate the process. These include the measurement of the backscattered echo amplitude, spectral and fractal analysis, wavelet decomposition, blood flowmetry and elasticity measurement. Attempts have been made to obtain more definitive data by multifeature analysis. Although some interesting results have been obtained, no approach seems yet to have reached the reliability necessary to support critical decisions concerning clinical management.

Similarly, accurate image segmentation has not been reliably achieved without at least a degree of intervention by a trained observer. This is hardly surprising, considering the inherently speckly nature of most ultrasonic images.

For further information, refer to Baldwin *et al* (2005), Chikui *et al* (2005), Coleman *et al* (2005), Mohamed *et al* (2005), Sarti *et al* (2005), Scheipers *et al* (2005), Schmitz *et al* (1999), Shankar *et al* (2002) and Tunis *et al* (2005).

3.2. Microscanning and intravascular ultrasonic scanning

Here, microscanning is defined as any imaging technique with a spatial resolution in the range 10–100 μm. For example, using pulse-echo ultrasound, a resolution in the order of 50 μm can be obtained with focused beams at frequencies of 40–60 MHz, corresponding to wavelengths of 37.5–25 μm. Typically, at these frequencies, the attenuation in soft tissues is between 2 and 10 dB mm^{-1}, so that the maximum depth of penetration is in the range 5–25 mm. Until now, most work has been done with mechanically scanned single-element transducers, with an inherent limitation on the frame rate. Recently, however, annular and linear array transducers have begun to be applied in real-time small animal imaging.

Intravascular ultrasonic scanning (IVUS) is an established clinical technique, using either mechanically scanned or cylindrical array transducers operating at about 20 MHz. Current systems produce radial scans. Forward-viewing systems are being developed and this is an area in which cMUTs (see section 2.1) may have early application.

In addition to their applications in humans, microscanners are proving to be useful in research applications with small animals, e.g., in phenotypic study, genetic research and drug development.

For further information, refer to Foster *et al* (2000), Knapik *et al* (2000) and Wang *et al* (2002).

3.3. Elasticity imaging

The goal of elasticity imaging is to map tissue properties such as Young's modulus, Poisson's ratio and viscosity. These properties are often modified by disease processes (e.g., malignant lesions are usually harder than their surrounding tissues).

The principal methods of ultrasonic elasticity imaging depend on the observation of tissue displacement (i.e., strain) in response to applied force (i.e., stress) resulting from externally

applied static or vibrating pressure (including cardiac pulsations in arteries) or from internally generated acoustic radiation force. The change in tissue stiffness with time can also be imaged: this is related to the viscoelastic properties of the tissue.

The spatial resolution of elasticity imaging is at least comparable with that of traditional pulse-echo B-scanning. It is a speckle-free technique. Seeing that manual palpation is one of the mainstays of clinical examination, elasticity imaging is already proving to be of significant practical importance.

For further information, refer to Doyley *et al* (2005), Gao *et al* (1996), Konofagou *et al* (2001), Nightingale *et al* (2002) and Righetti *et al* (2005).

3.4. Reflex transmission imaging

Reflex transmission imaging is the technique in which backscattered echoes gated from a tissue volume situated beyond the focal region of a strongly focused ultrasonic beam are integrated and displayed while the focal region is scanned through the tissue to be imaged. The amplitude of the received signal is dominated by the attenuation of the tissue in the focal volume. The technique works quite well when there is a suitably uniform volume of tissue beyond the image plane and when the intervening tissue is relatively homogeneous. Since it was originally demonstrated nearly 15 years ago, the technique has been largely unexplored but, recently, interest has been revived and its potential is now being more actively investigated, particularly when combined with other approaches, the performance of which may be enhanced by being able to compensate for attenuation.

For further information, refer to Green *et al* (1991).

3.5. Computed tomography

Ultrasonic computed tomography produces images by backprojection reconstruction from profiles of attenuation or speed acquired at multiple angles by scanning the tissue in a two-dimensional plane. The female breast and the long bones are obvious candidates to be imaged by this technique. Unfortunately, however, an ultrasonic beam is deviated by refraction and distorted by inhomogeneities in tissue. Consequently, the results which have so far been obtained have been rather disappointing. Like reflex transmission imaging (see section 3.4), however, ultrasonic CT could potentially produce data which might be used to correct aberrations in traditional B-scans.

For further information, refer to Duric *et al* (2005) and Lasaygues *et al* (2005).

3.6. Doppler tomography

In Doppler tomography, a wide (but thin) ultrasonic beam is rotated around the tissue to be imaged. The reflectors and scatterers within the tissue return echoes which are correspondingly Doppler shifted in frequency. The Doppler frequency spectra acquired at a set of angles around the tissue are equivalent to a set of cross-range profiles of the corresponding radial positions of the reflectors and scatterers and a two-dimensional image can consequently be produced by backprojection reconstruction. Doppler tomography uses continuous wave ultrasound and so it is a technique with narrow bandwidth and high sensitivity. Encouraging results have been obtained by amplitude-only reconstruction. It is anticipated that, by including phase data in the reconstruction, it should be possible to image, e.g., the female breast with a spatial resolution which significantly improves upon that which can be obtained by B-scanning at the same frequency.

For further information, refer to Liang *et al* (2001), Mensa *et al* (1983) and Wade *et al* (1978).

3.7. Photoacoustics and thermoacoustics

It has been demonstrated that thermally induced ultrasound can be produced by absorption of a pulse of light or of microwave electromagnetic radiation. In the case of tissue, the absorption of the pulse causes a rapid increase in temperature which results in localized expansion, according to the intensity of the pulse and the corresponding absorption coefficient. The phenomenon can be used for measuring the depth distribution of thermally induced ultrasonic signals from their times of arrival or, more generally, to produce three-dimensional images by reconstruction from the signals acquired by an array of ultrasonic sensors positioned around the tissue. Some encouraging results have been obtained with breast imaging.

For further information, refer to Feng *et al* (2001), Kruger (1994) and Manohar *et al* (2005).

4. Phantoms and quality assurance

Modern ultrasonic scanners employ solid-state electronic circuitry and are manufactured to meet tight performance specifications. Apart from the possibility of accidental damage to the relatively fragile ultrasonic probes, they are reliable and stable. Consequently, it might be supposed that there would be no need for periodic checks of imaging performance. This is not the case, however, for the very reason that imaging performance tends to deteriorate slowly and imperceptibly, usually as a result of minor damage to the probe (such as the failure of a single element in a transducer array with a large number of elements), or to slow drift in the settings of the electronics.

Pragmatically, the simplest and most direct method of checking the performance of an ultrasonic scanner is to display and examine the images which it produces from physical phantoms made up of tissue-mimicking materials of differing geometries, scattering and absorbing characteristics.

The simplest phantoms can be used to check the spatial resolution of the imaging system. More sophisticated phantoms are designed to test the contrast resolution. Elasticity imaging is amongst the other characteristics which can be assessed; flow and motion are other possibilities.

Except for the simplest of phantoms, the phantoms themselves do not have characteristics which can be depended upon not to change with time. Materials which closely mimic the ultrasonic properties of tissues are usually prepared by mixing, e.g., agar, gelatine and other substances which are themselves biological in origin and which are, consequently, themselves liable to become infected by bacteria or otherwise to deteriorate. The art of phantom manufacture is indeed akin to the art of preparing gourmet food.

Other aspects of quality assurance include the measurement of ultrasonic power, beam shape and intensity (spatial and temporal peaks and averages), as well as the relevant aspects of electrical, thermal and mechanical safety, infection control and so on.

For further information, refer to Browne *et al* (2003), Dandekar *et al* (2005), Goodsitt *et al* (1998), Poepping *et al* (2004) and Spirou *et al* (2005).

5. Safety considerations

Under certain exposure conditions, ultrasound may cause harmful bioeffects. Because of this, there is a hypothetical possibility that ultrasonic imaging may not be completely safe. Consequently, both regulatory authorities and prudent clinicians are concerned to balance

the likely benefits of the information which imaging provides against the risk of damage. Although this is the appropriate response to the question of the risk of adverse bioeffects due to ultrasonic exposure, the reality is that it is the consequences of misdiagnosis that are likely to be the greatest risk to the patient.

Regulatory agencies in some countries now oblige manufacturers to provide on-screen displays of quantities designated as the 'thermal index' (which relates to the risk of causing thermal damage) and the 'mechanical index' (which helps primarily to assess the likelihood of damage due to cavitation). These indices are for the guidance of clinicians in assessing risks and benefits and they provide reminders of the importance of applying the 'as low as reasonably achievable' (ALARA) principle in the context of justification for individual diagnostic investigations.

Although ultrasonic diagnosis has an impeccable record of safety in relation to the lack of adverse bioeffects, research into thermal, nonthermal and other mechanisms of interaction between ultrasound and biological systems continues to be an area of considerable activity. For example, with both the tendency for the ultrasonic exposure levels used by commercially available scanners steadily to be increased in order to obtain more information and the increasing use of microbubble contrast agents, there is fresh anxiety that safety may yet become a real concern.

For further information, refer to Abbott (1999), Fowlkes and Holland (2000), ter Haar and Duck (2000) and Nyborg (2002).

6. Conclusions

Looking back over the entire history of medical ultrasonic imaging, it is obvious that the truly major advances which have taken place have resulted from innovations in the applications of physics and engineering, rather than having been in response to the expressed aspirations of clinicians. In reality, what has happened is that physicists and engineers—who often are indistinguishable—have created new capabilities and clinicians, often sceptical and reluctant, have eventually embraced those technologies which have been perceived to be useful. To be even more controversial, it could be added that the utilities of new imaging technologies have hardly ever been scientifically proved before both clinicians and patients have demanded that they should be made available, so obvious to them have been their benefits.

Ultrasonic imaging stands alongside x-ray computed tomography and magnetic resonance imaging as one of the most disruptive of the medical applications of physics and engineering, having profoundly changed the practice of medicine and having brought immense benefits to mankind in the last half century. Speaking for ultrasound, but certainly not excluding other imaging techniques, the future is stimulating, exciting and challenging, and, for health and health care, the prospects are indeed brighter than ever before.

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Biography

Peter Wells (FRS, FREng, FMedSci) trained in electrical engineering, physics and zoology. Following a student apprenticeship with the General Electric Company in Coventry, his research career has been focused on the applications of ultrasound in medicine. For 25 years, he was Head of the Department of Medical Physics and Bioengineering at the United Bristol Healthcare NHS Trust and its predecessors, having previously been Professor of Medical Physics at what is now Cardiff University School of Medicine. He is now Distinguished Research Professor at Cardiff University, Visiting Professor at Imperial College London and Emeritus Professor at Bristol University.