



©Digital Stock 1997

# Current Status and Future Technical Advances of Ultrasonic Imaging

## *A Vital Diagnostic Tool that Has Great Opportunities for Further Development*

Thirty years ago, medical imaging was dominated by X-radiography, with a small contribution from radionuclide studies; neither X-ray computed tomography nor nuclear magnetic resonance imaging had yet been invented. Except, perhaps, for a few applications in obstetrics, gynecology, and cardiology, ultrasonic imaging was regarded merely as a laboratory curiosity. Now, because of remarkable advances in physics and engineering, more than one out of every four medical imaging studies is performed with ultrasound, and the proportion is increasing [1]. This article discusses current ultrasound technology in routine clinical practice, state-of-the-art technology in advanced practice, emerging technologies, and challenges in further developing the technologies.

### Pros and Cons of Ultrasound

The choice of the best imaging technique to help solve any particular clinical problem is actually based on factors such as resolution, contrast mechanism, speed, convenience, acceptability, and safety. For imaging soft tissues, ultrasound scores highly for all of these factors: spatial resolution of better than a millimeter can be obtained in abdominal scanning, tissue contrast is good (and may be enhanced by the use of contrast agents), it is a real-time method, it is convenient to use, it is highly acceptable to patients, and it is apparently safe. Only the most advanced equipment even approaches the price of that of other modalities.

The main disadvantages of ultrasound are that it does not work well in the presence of bone or gas, and the operator needs a high level of skill in both image

acquisition and interpretation. The physician seldom thinks in these terms, however, and typically chooses an imaging modality in the light of past experience with similar patients.

### Technology in Current Routine Clinical Practice

Figure 1 shows a typical modern ultrasonic scanner being used in a clinical investigation. Numerous publications (e.g., [2]) describe the principles involved. The operator is holding the probe in contact with the patient's skin; a water-based gel, smeared on the skin, excludes air that would otherwise prevent efficient ultrasonic coupling. The ultrasound is produced in response to electrical excitation of a transducer; the same transducer also produces electrical signals in response to ultrasonic echoes received from within the patient.

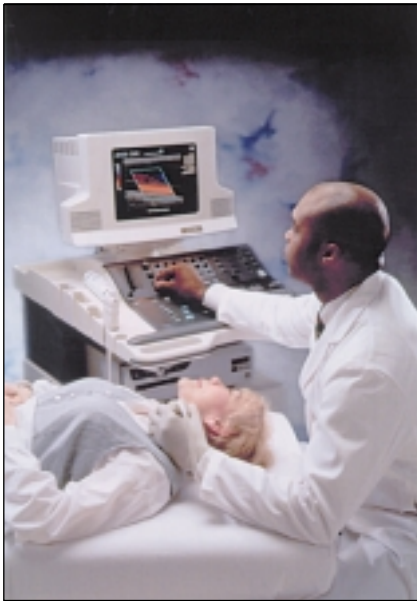
The ideal transducer would be perfectly matched to the tissues, have high efficiency as a transmitter and high sensitivity as a receiver, have a wide dynamic range to cope with both weak and strong echoes, and have a wide frequency response for short pulse operation. Piezoelectric transducers such as polarized lead zirconate titanate are used because, with appropriate backing and matching layers, they approach closer than any other currently available device to the ideal performance.

Although the simplest kind of probe uses a single disk transducer, which produces an ultrasonic beam whose central axis is normal to its surface, arrays of transducer elements are generally used to control the position of the ultrasonic beam and thus to acquire image information from the scanned tissue plane or volume. A typical linear array might have 128

---

Peter N.T. Wells  
Centre for Physics and  
Engineering Research in Medicine,  
University of Bristol

---



**1. A typical modern scanner in use. The operator is holding the ultrasonic probe in contact with the patient's skin and adjusting the controls of the scanner while observing the real-time image on the display.**

transducer elements, each 0.5 mm wide and 7.5 mm long, extending over a distance of 75 mm. Typically, the elements are excited in a group of 17 to form an aperture 10 mm long: this is an appropriate size to produce a beam that can be weakly focused in azimuth by an electronically generated time-delay profile across the aperture. By stepping the group along the array, one element at a time, in this example there are 111 discrete parallel beam positions separated from each other by about 0.6 mm.

Beam focusing in elevation is provided by a partial cylindrical lens attached to the front of the array. This means that focusing in elevation has to be at a fixed depth, both on transmission and reception. The same applies to focusing in azimuth of the transmitted beam. On reception, however, the focal length in azimuth can be swept along the beam continuously to coincide with the instantaneous position of the echo-producing tissue, by arranging for the time-delay profile across the transducer array aperture to be adjusted dynamically.

The ultrasonic beam from a transducer array can be steered through an angle by introducing a linear time-delay gradient across the aperture. If the beam is both to be focused and steered, a cylindrical time-delay profile needs to be superimposed on the linear gradient.

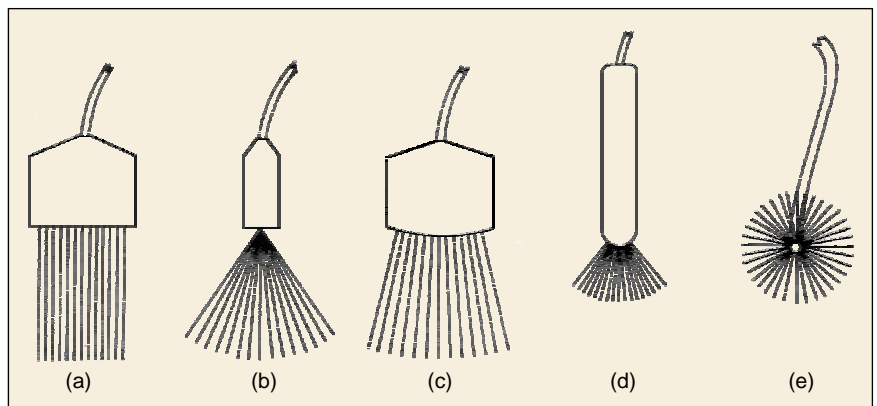
Although a linear array can be operated in this way, beam steering is more commonly used over the entire aperture of what is called a "phased array." This produces a sector scan format. A phased-array transducer typically has 64 elements in a 15 mm aperture, each element being about 0.2 mm wide and 10 mm long. The manufacture of such probes, with a separate electrical connection to each element and, often, multiplexing electronic circuits within the probe casing, and the specialized multicoaxial connecting cable, requires a high level of precision engineering. Indeed, it is partly because of the high rejection rate due to failures in manufacturing that transducer array probes are costly items.

A probe with a flat linear transducer array produces a scan with rectangular format, as illustrated in Fig. 2(a). The phased array produces a sector scan format [Fig. 2(b)]. The operation of the phased array depends on beam-steering electronics, however, and the circuitry for this is considerably more complicated than that required for linear array operation, even when electronically controlled dynamic focusing is provided with the latter. Because of the natural shape of the human body, flat linear array probes are often awkward to use. The smaller skin contact footprint and the sector format of phased-array probes provide much easier anatomical access, particularly when scanning the heart through intercostal spaces. By shaping a linear array to form a curvilinear probe, as shown in Fig. 2(c), the advantage of a fan scan format can be obtained without the need for complicated electronics, but at the expense of a somewhat longer footprint than that of the equivalent phased array. Curvilinear

**In the future, many physicians will carry ultrasonic scanners along with their other paraphernalia such as stethoscopes and ophthalmoscopes.**

probes are commonly used for abdominal scanning, and smaller versions mounted at the tips of extended probes are used in applications such as transvaginal scanning [Fig. 2(d)].

For intravascular ultrasonic scanning (IVUS), the transducer is mounted at the tip of a long (typically 1.2 m) flexible catheter with an outside diameter of about 3 mm. As shown in Fig. 2(e), the scan format is radial. Cylindrical transducer arrays, typically with 64 elements, have been developed for IVUS. The construction of these microminiature devices embodies many ingenious features. They are rather expensive and recommended only for single use. Because of this, less expensive probes, in which a small single-element disk transducer is mechanically rotated (by a flexible drive shaft passing



**2. Schematic drawings of ultrasonic probe shapes and beam scan patterns for (a) linear array, (b) phased array, (c) skin contact curvilinear array, (d) intracavitary curvilinear array, and (e) intravascular catheter devices.**

along the catheter, or by a micromotor at the tip) are currently, perhaps, more commonly used.

The point in the signal processing chain at which the signal is digitized is reflected, to some extent, in the cost of the scanner. In the least expensive scanners, analog circuitry may be used throughout, except that image storage, if provided for, is nowadays always digital. As the prices of integrated circuits have fallen and their performances enhanced, however, the trend has been toward earlier digitization in the signal processing chain. This is because digital signals can be precisely controlled; for example, time delays for beam

formation are free from drift, and control settings are completely reproducible.

The scanners that are currently used in routine clinical practice have features ranging from simple real-time gray-scale image display through duplex operation in which an ultrasonic pulsed Doppler sample volume can be positioned within the scan plane, using the image for anatomical localization, to obtain information about blood flow. Color flow imaging is another modality, an example of which is shown in Fig. 3. In this particular image, which is a single frame from a real-time sequence, the color is coded according to the blood-flow velocity. The color bar beside the image in-

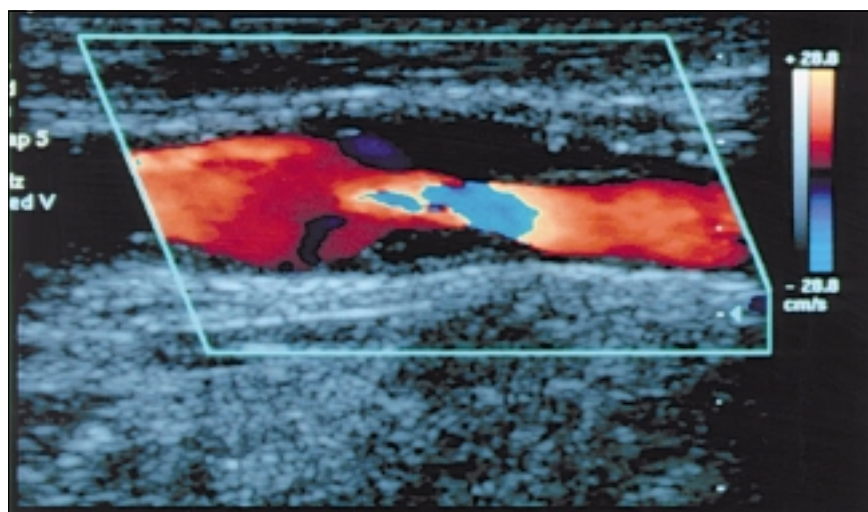
dicates that flow towards the probe is coded in hues of red and that flow away from the probe is coded in hues of blue. Essentially, the flow-velocity information is derived by a process equivalent to frequency spectrum analysis, and the variance of the frequency spectrum, which increases with increasing degrees of flow disturbance, may be displayed in green.

Color coding according to blood-flow velocity is very helpful in, for example, the investigation of blood flow through arterial stenoses, and within the heart. The method does have two important limitations: the magnitude and direction of the observed blood-flow velocity vector is dependent not only on the speed of blood flow but also on the angle between the directions of the blood flow and of the ultrasonic beam. Moreover, when the flow signal is weak, increasing the sensitivity of the receiver results in the display of spurious colors across a range of hues, caused primarily by the electronic noise generated within the circuits of the scanner. In order to mitigate these problems, a single color can be used, with its luminosity coded according to the power of the blood-flow signal. The disadvantage of this approach is that the velocity and velocity variance information is lost, but the sensitivity and noise immunity are both increased.

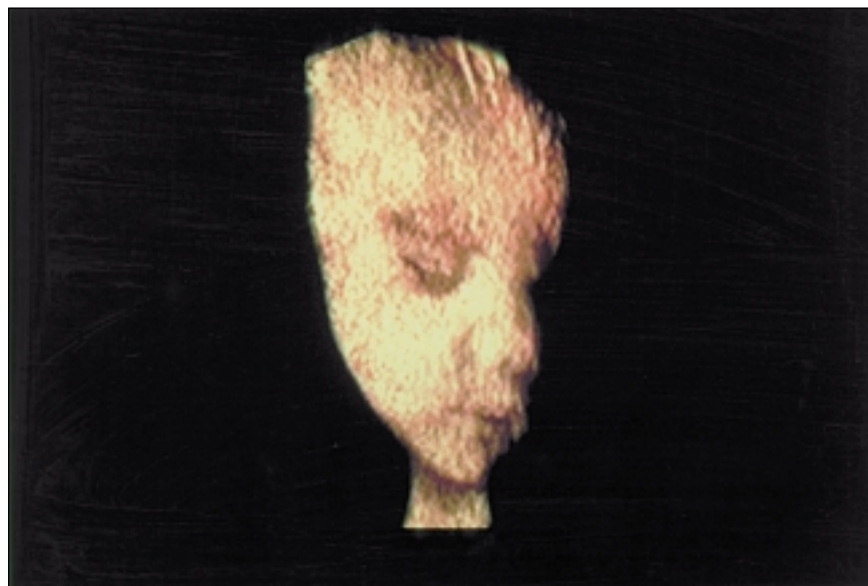
### State-of-the-Art Technology in Advanced Clinical Practice

One of the scanner characteristics that usually needs to be adjusted by the operator is the time-gain control, which determines the relationship between the gain of the receiver and the depth along the ultrasonic beam. This control compensates for the attenuation of ultrasound as it travels through tissue. In reality, of course, different kinds of tissues lie in the scan plane, and so a fixed time-gain control characteristic can only be a compromise. There is no obvious way of measuring the attenuation of the various tissues lying along each individual beam position. It has been observed, however, that the attenuation of tissue seems to be correlated with the amplitude of the echo that it backscatters. This relationship forms the basis of an adaptive time-gain control circuit [3], which seems to be able to produce improved images.

Because of the coherent nature of the ultrasonic scattering phenomenon, ultrasonic images are characterized by speckle [4]. It would appear to be sensible to reduce speckle in the image, provided that



3. Color flow image of carotid artery. The walls of the artery and the adjacent tissues are shown in gray scale. Within the parallelogram box, which indicates the orientation of the ultrasonic beams in the scan plane, blood flow is displayed in color, coded according to velocity. The narrowing of the artery, due to atherosclerotic plaque, causes flow disturbance.



4. Three-dimensional rendering of a fetal face in utero. Other structures have been segmented out of the image to provide a clear view.

image texture that might distinguish one tissue from another is not lost. Speckle can be reduced by summing uncorrelated images of the scan plane, or by adaptive filtering [5]. The improvements that result remain controversial but, if texture is not being used for tissue identification, speckle reduction does reduce one of the distractions in image interpretation.

With a one-dimensional (1-D) transducer array, electronically controlled beam focusing (and steering) is limited to the azimuth. What focusing there is in elevation is provided by a partial cylindrical lens attached to the front face of the transducer, and the focal length is fixed. It is possible, however, to provide a degree of electronically controlled (and hence, dynamic) focusing in azimuth if the individual elements in a 1-D array are split into a minimum of three. This approach certainly can result in thinner sections [6]; but it should be realized that this may not always be an advantage when trying to interpret anatomical information.

Imaging specialists have developed skill in exploring three-dimensional (3-D) anatomy by means of two-dimensional (2-D) scans. This skill is not shared by others, and complicated anatomy may be misinterpreted even by imaging specialists. For these reasons, 3-D image acquisition and display systems have been developed [7]. Figure 4 is an example of a 3-D image. The data may be acquired "freehand" with either a 2-D scanning probe fitted with a nonrestraining positional measurement system, the controlled movement of a 2-D scanning probe, or a 2-D array that can electronically control the beam position in the 3-D tissue volume.

Color flow-imaging systems are designed to identify regions in the scanned tissues in which there is blood flow [8]. Display of the stronger signals from moving solid tissues is suppressed. The movement of solid tissues, however, may have diagnostic significance: for example, dyskinesia is associated with myocardial infarction. In tissue Doppler imaging [9], the signal processing is arranged to color-code the display of solid tissue according to velocity.

In many situations, ultrasonic imaging can be enhanced by the use of contrast agents [10]. For example, the gas that is normally present in the gut can be displaced by contrast agent. The echogenicity of blood can be increased by the administration of a contrast agent consisting of a suspension of gas-filled

microbubbles, which can even be small enough to enter the systemic circulation after intravenous injection. Being gas-filled, microbubbles are strong scatterers: they scatter most strongly when they are of resonant size, which, depending on the characteristics of their outer shell, is at diameters of a few micrometers at low megahertz frequencies.

Microbubble contrast agents have nonlinear compressibility. This means that the scattered ultrasound contains harmonics of the transmitted frequency, increasingly with increasing amplitude. Consequently, under appropriate circumstances, the receiver can be adjusted to receive echoes at twice the transmitted frequency (the second harmonic) [11]. The advantages are that if contrast agent is present, its echoes are enhanced and the tissue echoes are reduced. Also, since the side-lobes of the transmitting and receiving beam have different directivity functions, image clutter is reduced and contrast is improved. This second advantage can be obtained even without contrast agent, because of the nonlinearity of the tissues themselves, provided that the transmitted amplitude is sufficiently great. Nonlinear imaging is the subject of much contemporary research, and numerous ingenious ultrasonic pulsing schemes are being explored.

### Emerging Technologies

In current clinical practice, the patient is usually brought to the scanner. This is both because scanners are quite substantial pieces of equipment and also because this approach matches the strategy for coping with the workload in the imaging department, whatever the imaging modality. Recently, however, physically small and easily portable scanners with excellent performance have begun to become available. It seems certain that, in the future, many physicians will carry ultrasonic scanners along with their other paraphernalia such as stethoscopes and ophthalmoscopes. Physicians will have to learn how to interpret the images, but, properly managed, this shift in practice will be greatly to the benefit of the patients.

By increasing the ultrasonic frequency in pulse-echo imaging, the spatial resolution can be increased, but at the expense of depth of penetration. At a frequency of 3 GHz, the wavelength is 500 nm, and a scanning acoustic microscope (SAM) with a diffraction-limited focal spot can provide the same resolution as an optical

## High-resolution imaging with a scanner mounted at the tip of a needle is another interesting possibility.

microscope [12]. The SAM has never become a commonly used instrument in histopathology, probably because of its cost and complexity. Recently, however, the potential of 50-100 MHz imaging has begun to be explored [13]. Typically, a 5 mm tissue cube can be imaged in three dimensions with a spatial resolution of around 30  $\mu\text{m}$ . Various strategies are being developed to reduce the scanning time, which currently may otherwise be as long as 1 h. Two-dimensional imaging can, in principle, be in real time, and thus in-vivo applications in ophthalmology and dermatology are already established. High-resolution imaging with a scanner mounted at the tip of a needle is another interesting possibility.

Pulse-echo imaging uses the aperture of a single transducer, or a transducer array, to form the ultrasonic beam. An alternative approach is separately to acquire signals corresponding to a (large) number of independent points or lines within the aperture, and then artificially to synthesize the echoes received from multiple beam directions within the scanned section or volume of tissue; this is a process called "synthetic aperture imaging." In principle, since many beam directions can be simultaneously synthesized, this technique can be faster than pulse-echo imaging with the same line density and resolution. The technique has been tried, with limited success, with linear transducer arrays [14], and it forms the basis of one of the signal processing approaches with miniature cylindrical arrays used in IVUS.

The scattering of ultrasound by tissue is often anisotropic [15]. For example,

# One challenge is to identify ultrasonic characteristics at the genetic level and to devise methods for imaging and measuring them.

muscle fibers scatter more when the ultrasonic beam is perpendicular to the fiber axes than when it is parallel. Malignant tumor tissue tends to be disorganized, and so the presence of a tumor in normally anisotropic tissue may be inferred from the development of isotropic scattering.

The measurement of tissue blood perfusion by ultrasound has so far proved to be problematic. Capillary flow is characterized by very low velocity and it is difficult to separate the Doppler signals caused by blood flow from those due to solid tissue movement. A multibeam multifrequency approach [16] is promising, however, and the use of contrast agents may also lead to a clinically applicable method in appropriate circumstances.

Pulse-echo ultrasonic imaging basically provides information about the scattering properties of tissue. The attenuation of tissue can be inferred from shadowing or echo enhancement, and from its correlation with scattering strength, but it cannot be measured with traditional methods. Reflex transmission imaging, however, does provide a 2-D image of relative attenuation in a plane scanned point-by-point by the focal spot of a tightly focused beam [17]. The basis of the method is that ultrasound backscattered from a gated tissue volume beyond the focus changes relatively slowly as different tissues enter and leave the gated volume. It is the attenuation by the tissue in the focal volume that dominates in determining the amplitude of the received signal. Appropriate conditions for reflex transmission imaging

could be established, for example, in scanning ex-vivo tissue specimens and in skin scanning.

In computed tomography, ultrasound is transmitted from a transducer on one side of the tissue to a receiving transducer on the other side, and a set of projections of velocity or attenuation is acquired. This method depends on the validity of the assumption that line-of-sight propagation is maintained across the tissue. The image is then formed by computed backprojection reconstruction. Anatomical restrictions limit the applicability of the method and, until recently, the results have been rather disappointing. By using CT-derived data of ultrasound speed, however, B-scan misregistration can be corrected, with encouraging results [18]. This method may also be applicable for scanning small histological specimens.

When a subablation-amplitude nanosecond-duration laser pulse is absorbed in tissue, ultrasonic thermoelastic waves are produced. This is the basis of photoacoustic tissue characterization. The optical properties of the tissue affect the amplitudes and temporal distributions of the ultrasound, with depth information provided by the time-of-arrival of the ultrasound following the delivery of the light pulse [19]. This method has considerable potential in, for example, the characterization of arterial plaques and the control of intravascular angioplasty and plaque ablation. A somewhat similar approach uses microwave electromagnetic pulses to induce ultrasound: tomographic images have been made of excised lamb kidney with this method [20].

Different tissues have different mechanical properties. For example, malignant tumors are usually harder than normal tissue. Several methods of ultrasonic elasticity imaging have been demonstrated. In vibration amplitude sonoelastography, a low-frequency (20-1000 Hz) vibration is externally applied to excite internal tissue motion, of which an image is produced by Doppler detection [21]. In vibration phase-gradient sonoelastography, both the amplitude and the phase of externally excited low-frequency internal tissue motion are measured. By assuming that viscosity is negligible at low frequencies, and that shear waves predominate [22], images of Young's modulus have been obtained for different degrees of muscle contraction. In the method of compression strain elastography, the tissue is externally compressed, and pre- and postcompression ul-

trasonic A-scan line pairs are cross correlated to produce a set of strain profiles [23]. In an ingenious variant of this method [24], an IVUS system has been used to obtain strain elastograms of diseased arteries in vitro, with the change in strain being produced by change in (blood) pressure. When the tissue displacements are large (around 10 wavelengths), compression strain elastography is possible if small displacements are measured incrementally [25]. Finally, displacement can be observed by speckle tracking [26]. Whatever methodology is used, elasticity imaging is potentially very significant because of the excellent tissue discrimination that it may provide.

Unlike CT and MR images (in which, for instance, bone can readily be distinguished from soft tissue), ultrasonic images generally cannot easily be automatically "segmented" into separate anatomical or structural elements. (An exception is the lumens of blood vessels, where they can be delineated by the presence of color-coded flowing blood.) This is because ultrasonic images are fundamentally "noisy," as the coherent nature of ultrasound gives rise to speckle. Progress is being made, however, in developing active contour models [27], integrated edge maps [28], and minimum cross-entropy thresholding [29].

## Grand Challenges

Following this overview of technologies that are already used in clinical practice, both routine and advanced, and which are currently emerging with potential applications, it is possible to identify several grand challenges in ultrasonic imaging that researchers in science and engineering might now seek to solve.

### Targeted Contrast Agents

Contemporary ultrasonic contrast agents generally fall into two categories. The gas-displacing agents, which really are misnamed as contrast agents because they do not themselves change the ultrasonic characteristics of tissue, simply occupy spaces that otherwise contain gas, and so enhance the visualization of deeper tissues. Microbubble contrast agents enhance and modify the scattering of ultrasound by blood or are introduced into fluid-filled spaces to make them more visible. There is, however, yet another category of contrast agents. These agents are targeted differently to different tissues, by being involved in physiologic or pathologic pro-

cesses. For example, blood-borne perfluorochemical particles concentrate in reticuloendothelial tissue and increase its echogenicity [30]. The difficulty is that these particles are much weaker scatterers than microbubbles, so that large quantities need to be delivered. The grand challenge is to develop efficient contrast agents that are effectively targeted to clinically relevant sites and thus safe to substitute for tests that currently can only be performed by nuclear medicine using radioactive tracers.

### **Real-Time Three-Dimensional Imaging**

Ultimately, it is the propagation speed of ultrasound in tissue that limits the rate at which ultrasonic imaging can be performed. In practice, this means, for example, that an image sector with a depth of 150 mm and consisting of 250 lines (i.e., 250 separate ultrasonic beam positions) can be acquired in 50 msec, which corresponds to an image frame rate of 20 per second. Being faster than the persistence of vision, truly real-time 2-D scanning is possible. This is not the case with a simple approach to 3-D scanning. In the extension to three dimensions of the example that has just been considered, 250 separate 2-D scans are needed to achieve isotropic spatial line density, and the corresponding image acquisition time is 12.5 sec. In practice, because the resolution in elevation is worse than that in azimuth, and with some sacrifice in line density, simple 3-D imaging at a rate of around one frame per second is realistic. The grand challenge here is to develop techniques for true real-time 3-D imaging: simultaneous multiple beam reception [31], synthetic aperture scanning [14], and holography [32] are among the methods that might now be re-explored.

### **Molecular Imaging**

The objective of contemporary ultrasonic imaging techniques is to obtain information about structure and function, for the purpose of disease screening, detection, and characterization. The images depict the spatial and temporal distributions of differences in tissue density, propagation speed, attenuation, flow, motion, directivity, and optical and elastic properties. Contemporaneously with the development of these imaging methods, huge advances have been made in genome research, the understanding of molecular mechanisms of disease, and in

the development of innovative therapies at the genetic level [33]. The new concept of molecular imaging depends on image contrast that represents specific molecules and structural characteristics at the subcellular level. As an example of what may enable ultrasonic imaging to become an essential tool in the practice of molecular medicine, it has been demonstrated that apoptotic changes may be detected by ultrasonic microscanning [34]. The grand challenge is to identify ultrasonic characteristics at the genetic level and to devise methods for imaging and measuring them.

### **A New Philosophy of Imaging**

An image is a representation of the reality. An ultrasonic image can do no more than convey information to the observer concerning structure and function as represented by the ultrasonic characteristics of the tissue. Moreover, the image is degraded by artifacts. In general, therefore, ultrasonic images are not readily understood by people not trained to do so, and only imaging experts can interpret them. Given one or more ultrasonic images, however, an imaging expert and a medical artist can create a picture of what would be seen if the structure were to be exposed to direct vision, which even untrained people can immediately comprehend. Analysis of this process reveals that it does not involve any intelligence but only pattern recognition and graphical reconstruction [35]. The grand challenge is to devise a system to display pictures, even if imperfect, from ultrasonic (and other) images and tests, and thus to make the relevant information accessible without the need for intermediate interpretation.

### **Health Technology Assessment**

When a new health technology becomes available, and ultrasonic imaging is no exception, its actual value in patient management may not be immediately obvious. In the past, new technologies were often allowed to diffuse into widespread clinical use without any proper evaluation. However, as resources have become scarcer, and as the need for efficacy to be established has become increasingly recognized [36], health service managers have sought to control the situation. The dilemma is that technologies change during the course of evaluation, and that patients should not be deprived of beneficial technologies during the time that their

**Although the primary  
role of ultrasonic  
imaging is in  
diagnosis, it also has  
important applications  
in monitoring the  
progression and  
regression of disease.**

cost-effectiveness is being demonstrated. The grand challenge is to develop methods of health technology assessment for ultrasound (and other technologies) that can reconcile the necessity for prudence with the imperative of progress.

### **Conclusions**

Ultrasonic imaging is an essential component of modern medical practice. It is complementary to other imaging modalities; often, it is the best or even the only applicable method. Although the primary contemporary role of ultrasonic imaging is in diagnosis, the method also has important applications in monitoring the progression and regression of disease, in some areas of screening, and in interventional procedures, both for localization and for guidance. Its safety record is impeccable.

There are tremendous opportunities for the further development of ultrasonic imaging, many of which are the subjects of contemporary research. There can be no doubt that much remains still to be discovered and that very significant advances will continue to be made for the foreseeable future.

### **Acknowledgment**

Figures 1, 3, and 4 were kindly provided by Advanced Technology Laboratories, Bothell, Washington, USA.



*Peter N.T. Wells* is director of the Centre for Physics and Engineering Research in Medicine at the University of Bristol and chief physicist to the United Bristol Healthcare National Health Service

Trust. He is a past-president of the British Medical Ultrasound Society, the British Institute of Radiology, and the Institute of Physics and Engineering in Medicine. His main research interest is in the medical applications of ultrasound and he is editor-in-chief of *Ultrasound in Medicine and Biology*, the official journal of the World Federation for Ultrasound in Medicine and Biology. Professor Wells has published 15 books, 104 papers in peer-reviewed journals, and 170 other articles. He is a Fellow of the Royal Academy of Engineering.

**Address for Correspondence:** Peter N.T. Wells, Centre for Physics and Engineering Research in Medicine, University of Bristol, Bristol General Hospital, Bristol BS1 6SY, UK. Tel: +44 117 928 6274. Fax: +44 117 928 6371. E-mail: peter.wells@bristol.ac.uk.

## References

1. **WFUMB:** World Federation for Ultrasound in Medicine and Biology News, vol. 4, no. 2. *Ultrasound Med Biol* 23: following p. 974, 1997.
2. **Wells PNT:** Ultrasonic imaging of the human body. *Rep Prog Phys* 62: 671-722, 1999.
3. **Hughes DI and Duck FA:** Automatic attenuation compensation for ultrasonic imaging. *Ultrasound Med Biol* 23: 651-664, 1997.
4. **Wells PNT and Halliwell M:** Speckle in ultrasonic imaging. *Ultrasonics* 19: 225-229, 1981.
5. **Bamber JC and Daft C:** Adaptive filtering for the reduction of speckle in ultrasonic pulse-echo images. *Ultrasonics* 24: 41-43, 1986.
6. **Whittingham TA:** New and future developments in ultrasonic imaging. *Br J Radiol* 70: S119-S132, 1997.
7. **Nelson TR and Pretorius DH:** Three-dimensional ultrasound imaging. *Ultrasound Med Biol* 24: 1243-1270, 1998.
8. **Wells PNT:** Ultrasonic colour flow imaging. *Phys Med Biol* 39: 2113-2145, 1994.
9. **Hoskins PR and McDicken WN:** Colour ultrasound imaging of blood flow and tissue motion. *Br J Radiol* 70: 878-890, 1997.
10. **Goldberg BB, Liu J-B, and Forsberg F:** Ultrasound contrast agents: A review. *Ultrasound Med Biol* 20: 319-333, 1994.
11. **Burns PN:** Harmonic imaging with ultrasound contrast agents. *Clin Radiol* 51: 50-55, 1996.
12. **Lemons RA and Quate CF:** Acoustical microscopy: Biomedical applications. *Science* 188: 905-911, 1975.
13. **Turnbull DH, Ramsay JA, Shivji GS, Bloomfield TS, From J, et al.:** Ultrasound backscatter microscope analysis of mouse melanoma progression. *Ultrasound Med Biol* 22: 845-853, 1996.
14. **Ylitalo J:** On the signal-to-noise ratio of a synthetic aperture ultrasound imaging method. *Eur J Ultrasound* 3: 277-281, 1996.
15. **Insana MF, Hall TJ, and Fishback JL:** Modeling acoustic backscatter from kidney microstructure using an anisotropic correlation function. *J Acoust Soc Am* 97: 649-655, 1995.
16. **Jansson T, Persson HW, and Lindström K:** Estimation of blood perfusion using ultrasound. *J Eng Med* 213: 91-106, 1999.
17. **Green PS, Ostrem JS, and Whitehurst TK:** Combined reflection and transmission ultrasound imaging. *Ultrasound Med Biol* 17: 283-289, 1991.
18. **Jago JR and Whittingham TA:** Experimental studies in transmission ultrasound computed tomography. *Phys Med Biol* 36: 1515-1527, 1991.
19. **Beard PC and Mills TN:** Characterisation of post mortem arterial tissue using time-resolved photoacoustic spectroscopy at 436, 461 and 532 nm. *Phys Med Biol* 42: 177-198, 1997.
20. **Kruger RA, Reinecke DR, and Kruger GA:** Thermoacoustic computed tomography—technical considerations. *Med Phys* 26: 1832-1837, 1999.
21. **Lerner RM, Huang SR, and Parker KJ:** "Sonoelasticity" images derived from ultrasound signals in mechanically vibrated tissues. *Ultrasound Med Biol* 16: 231-239, 1990.
22. **Levinson SF, Shinagawa M, and Sato T:** Sonoelastic determination of human skeletal muscle elasticity. *J Biomech* 28: 1145-1154, 1995.
23. **Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, and Li X:** Elastography: A quantitative method for imaging the elasticity of biological tissues. *Ultrason Imag* 13: 111-134, 1991.
24. **de Korte CL, van der Steen AFW, Cespedes EI, and Pasterkamp G:** Intravascular ultrasound elastography in human arteries: Initial experience in vitro. *Ultrasound Med Biol* 24: 401-408, 1998.
25. **O'Donnell M, Skovoroda AR, Shapo BM, and Emelianov SY:** Internal displacement and strain imaging using ultrasonic speckle tracking. *IEEE Trans Ultrason, Ferroelect, Freq Contr* 41: 314-325, 1994.
26. **Walker WF, Friemel BH, Laurence NB, and Trahey GE:** Real-time imaging of tissue vibration using a two-dimensional speckle tracking system. In: *Proc IEEE Ultrasonics Symp* pp. 873-877, 1993.
27. **Chalana V, Linker DT, Haynor D, and Kim Y:** A multiple active contour model for cardiac boundary detection on echocardiographic sequences. *IEEE Trans Med Imag* 15: 290-298, 1996.
28. **Aarnik RG, Pathak SD, de la Rosette JJMCH, Debruyne FMJ, Kim Y, and Wijkstra H:** Edge detection in prostatic ultrasound images using integrated edge maps. *Ultrasonics* 36: 635-642, 1998.
29. **Zimmer Y, Tepper R, and Akselrod S:** A two-dimensional extension of minimum cross entropy thresholding for the segmentation of ultrasound images. *Ultrasound Med Biol* 22: 1183-1190, 1996.
30. **Mattrey RF, Scheible FW, Gosink BB, Leopold GR, Long DM, and Higgins CB:** Perflouroctylbromide: A liver/spleen-specific tumor-imaging ultrasound contrast material. *Radiology* 145: 759-762, 1982.
31. **Shattuck DP, Weinschenker MD, Smith SW, and von Ramm OT:** Explososcan: A parallel processing technique for high speed ultrasonic imaging with linear phased arrays. *J Acoust Soc Am* 75: 1273-1282, 1984.
32. **Chivers RC:** B-scanning and holography in ophthalmic diagnosis. *Ultrasonics* 12: 209-213, 1974.
33. **Weissleder R:** Molecular imaging: Exploring the next frontier. *Radiology* 212: 609-614, 1999.
34. **Czarnota GJ, Kolios MC, Vaziri H, Benchimol S, Ottensmeyer FP, et al.:** Ultrasonic biomicroscopy of viable, dead and apoptotic cells. *Ultrasound Med Biol* 23: 961-965, 1997.
35. **Sarvazyan AP, Lizzi FL, and Wells PNT:** A new philosophy of medical imaging. *Med Hypoth* 36: 327-335, 1991.
36. **Wells PNT, Garrett JA, and Jackson PC:** Assessment criteria for diagnostic imaging technologies. *Med Prog Technol* 17: 93-101, 1991.