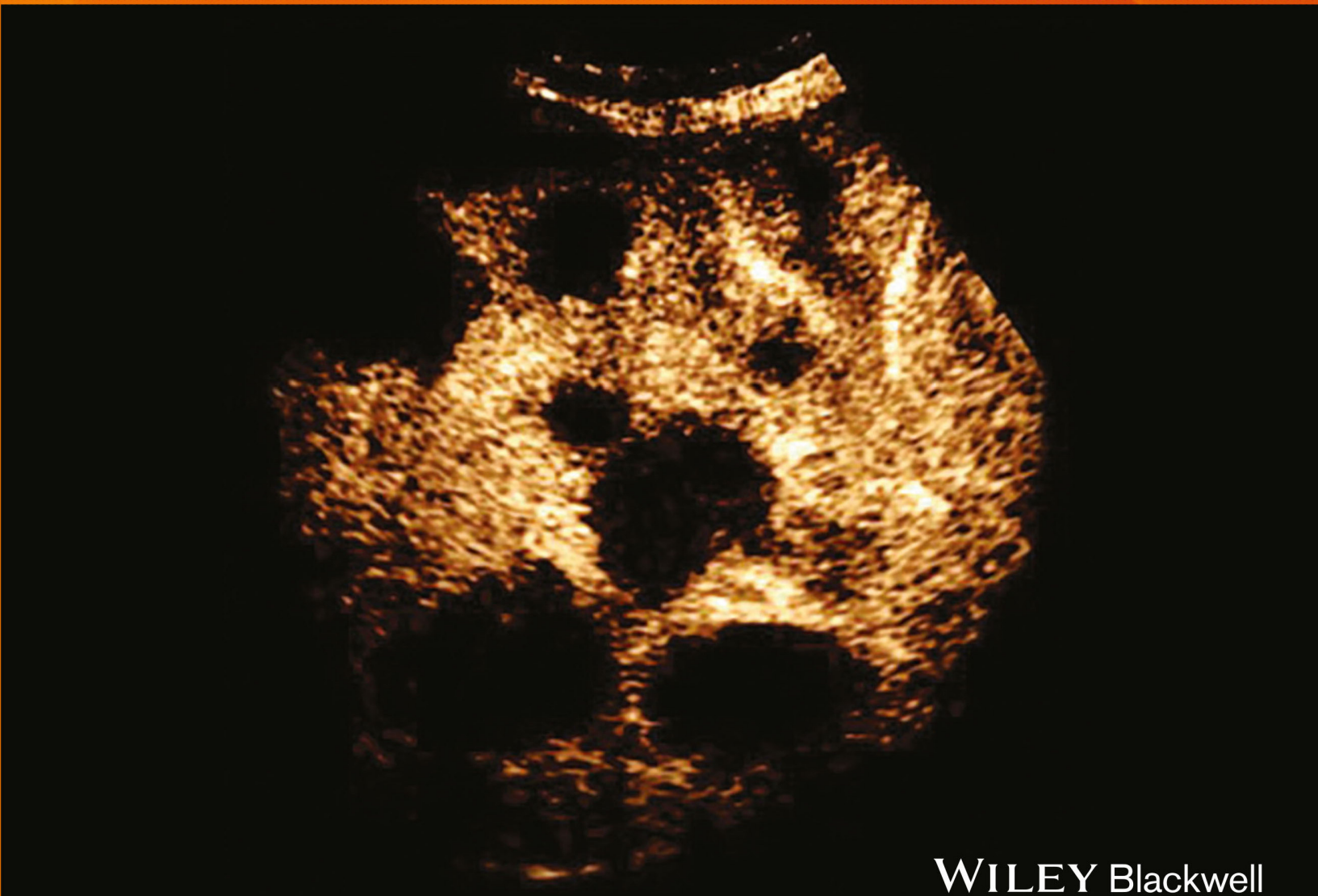
Liver Ultrasound

From Basics to Advanced Applications

Edited by
Adrian K.P. Lim • Matteo Rosselli



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Forewords

It gives me great pleasure to write the foreword for this very exciting book. Every practical aspect of the discipline has been covered by an energetic team of experts, providing an easily accessible manual for a branch of medical imaging that for some non-experts has been seen as highly specialised and difficult to unlock.

Professor Adrian K.P. Lim is a Professor of Medical Imaging at Imperial College London who, over the years, has majored on new ultrasound techniques, improving visualisation and discrimination of malignant from non-malignant lesions. Dr Matteo Rosselli has worked at the Institute for Liver and Digestive Health at University College London for many years. Together with Professor Adrian K.P. Lim, he has organised the International Hepatology Ultrasound Course at the Royal Free Hospital in London with an active opportunity for 'hands-on' experience for each delegate.

It was this practical approach to teaching and problem solving that has informed this easily digestible book. As a hepatologist who has relied on the expertise of Professor Adrian K.P. Lim and Dr Matteo Rosselli for important diagnostic advice on a tidal wave of patients over the years, it is gratifying to see their knowledge opened up to a wider audience.

Professor Simon Taylor-Robinson
Professor of Translational Medicine
Imperial College London

Undoubtedly, Adrian K.P. Lim and Matteo Rosselli are genuine experts in the field of liver ultrasonography. Together they combine the skills and knowledge of the clinical radiologist with the domain expertise of the practicing hepatologist to address an aspect of patient care which is crucial in the day-to-day management of patients with liver disease. Not only are they experts in the art and science of liver ultrasound but, as illustrated in this book, they are also world class teachers of liver ultrasound.

As a clinical hepatologist at St Marys Hospital London for over 30 years and a professor of hepatology at Imperial College, I have witnessed and appreciated the evolution of liver ultrasound and the increasing dependence on this diagnostic technology in hepatology. Whilst most hepatologists, usually with a gastroenterology training, understand the strengths and limitations of endoscopy, the same cannot be said of ultrasonography. Unfortunately, relatively few hepatologists have mastered ultrasound and consequently fail to fully comprehend the full versatility of this crucial diagnostic tool. Within this book lies an opportunity to correct this deficiency.

Whilst no one can be expected to master a sophisticated skill such as ultrasound without the guidance and training provided by an expert, Adrian K.P. Lim and Matteo Rosselli's 'Liver Ultrasound' goes a long way in providing the information required to get started in this field. The first few chapters provide the novice with the essentials of ultrasound physics, liver anatomy and indeed the anatomy of the ultrasound machine, appropriately termed 'knobology'. Subsequent chapters deal with the common and, in some cases less common, causes of liver disease with focus on focal liver lesions, biliary tract disease, vascular disease and ultrasound in chronic liver disease. This book also deals with relatively new developments in ultrasound including the use of shearwave elastography for assessment of liver fibrosis and microbubble ultrasound for characterisation of space-occupying lesions. The practical nature of this book is illustrated by the chapter on interventional radiology techniques which includes a guide to managing patients with coagulopathy requiring invasive procedures - frequently a source of tension between radiologist and hepatologist.

This is a book which I would strongly recommend to all trainee hepatologists and gastroenterologists. It really should be considered as essential reading for those hepatologists planning to undertake training in liver ultrasound and should definitely be included in the induction pack for radiology trainees. I would like to see an era when all hepatologists undertook their own liver ultrasounds. This book may be one of the catalysts which help to make this happen.

Professor Mark Thursz
Professor of Hepatology and Head of Department
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It is with great pleasure that I introduce to you this book on Liver Ultrasound conceived and led by Adrian K.P. Lim and Matteo Rosselli. The book includes chapters ranging from very basic physical concepts of medical ultrasound to the most updated guidelines for the use of ultrasonography in the clinical management of patients with liver diseases. Since my early training as a clinical hepatologist, I have witnessed the progressive technical development of this field and how ultrasonography has become an essential instrument in everyday clinical practice. The latest developments, including the use of elastography for the assessment of liver tissue fibrosis and contrast agents for the characterization of liver lesions, have made ultrasonography a solid omni-comprehensive asset in Hepatology.

The concept of the book derives from the success of the series of International Liver Ultrasound workshops organized at the Royal Free Hospital in London in the past ten years and is directed at providing a written and illustrated basis to everybody who is interested in developing skills in liver ultrasonography and relative clinical applications. The book is obviously directed to radiologists and sonographers but, most importantly, to trainees in Hepatology and hepatologists, who will have the highest professional advantage by becoming independent users of ultrasonography.

In conclusion, I am truly enthusiastic about this book, and I wish huge success to all those who wish to become expert users of this technology.

Professor Massimo Pinzani
MD, PhD, FRCP, FAASLD, MAE
Sheila Sherlock Chair of Hepatology
University College London, Royal Free Hospital

Preface

The origins of this book stemmed from a series of workshops that we put together and the realisation that there was an appetite for most clinicians and allied health professionals to learn how to scan a liver. While most of us learn via mentors and on the job, rarely are the basics, the 'tips and tricks', put into words. Instead, these nuggets of information tend to be passed on from generation to generation by word of mouth.

With ultrasound becoming the modern-day 'stethoscope', the initial aim of this book was to provide an 'all you need to know' about liver ultrasound, from the basics to advanced practice. As the chapters developed, it progressed from a relatively basic to intermediate-level book into one that encompasses a wide range of diseases. Our esteemed co-authors also provided in-depth knowledge on the multifaceted aspects of liver pathology, its clinical background, and how to apply the latest and advancing technologies.

Overall, it has turned into a book for the beginner to take with them through their journey and medical career, offering a pictorial review of both common and uncommon diseases. We hope this will serve the current and future generations of multidisciplinary liver ultrasound imagers well.

To our past, present, and future colleagues and students – thank you for teaching, helping, and inspiring us to write this book!

Adrian K.P. Lim and Matteo Rosselli

About the Companion Website

This book is accompanied by a companion website.

www.wiley.com/go/LiverUltrasound

This website includes:

- Video clips

1

Getting Started

Ultrasound Physics and Image Formation

Sevan Harput[1], Xiaowei Zhou[2], and Meng-Xing Tang[3]

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What Is Ultrasound?

Ultrasound refers to an acoustic wave whose frequency is greater than the upper limit of human hearing, which is usually considered to be 20 kHz. Medical ultrasound operates at a much higher frequency range (generally 1–15 MHz) and it is inaudible. Medical ultrasound images are produced based on the interaction between the ultrasound waves with the human body. For this reason, producing and interpreting an ultrasound image require an understanding of the ultrasound waves, their transmission and reception by sensors, and the mechanisms by which they interact with biological tissues.

Ultrasound Waves

Unlike electromagnetic waves used in optical imaging, X-ray, and computed tomography (CT), ultrasound waves are mechanical waves that require a physical medium to propagate through. For example, ultrasound waves can travel in water or human tissue, but not in a vacuum. Ultrasound waves transport mechanical energy through the local vibration of particles. In other terms, an ultrasound wave propagates by the backwards and forwards movement of the particles in the medium. It is important to note that while the wave travels, the particles themselves are merely displaced locally, with no net transport of the particles themselves. For example, if a lighted candle is placed in front of a loudspeaker, the flame may flicker due to local vibrations, but the flame would not be extinguished since there is no net flow of air, even though the sound can travel far away from the speaker [1]. While propagating in a medium, both the physical characteristics of the ultrasound wave and the medium are important for understanding the wave behaviour. Therefore, this section will first introduce the relevant physical processes and parameters that affect ultrasound wave propagation.

Ultrasound Wave Propagation

There are many types of acoustic waves, such as longitudinal, shear, torsional, and surface waves. The mechanical energy contained in one form of an acoustic wave can be converted to another, so most of the time these waves do not exist in isolation. However, for the sake of simplicity we will only describe the longitudinal or compressional waves, which are most commonly used in B-mode and Doppler imaging.

The propagation of longitudinal ultrasound waves is illustrated in Figure 1.1 using discrete particles. As we know, human tissue is not made up of discrete particles, but rather a continuous medium with a more complicated structure. This is merely a simplified physical model to explain wave propagation. During the wave propagation, particles are displaced due to the acoustic pressure in parallel to the direction of motion of the longitudinal wave, as illustrated in Figure 1.1a–c. When the pressure of the medium is increased by the wave, which is called the compression phase, particles in adjacent regions move towards each other. During the reduced pressure phase (rarefaction), particles move apart from each other. During these two phases, the change in the concentration of particles changes the local density, shown in Figure 1.1d as the higher-density regions with darker colours. This change in local density can be related to the change in acoustic pressure, which is also proportional to the velocity of the particles, Figure 1.1e.

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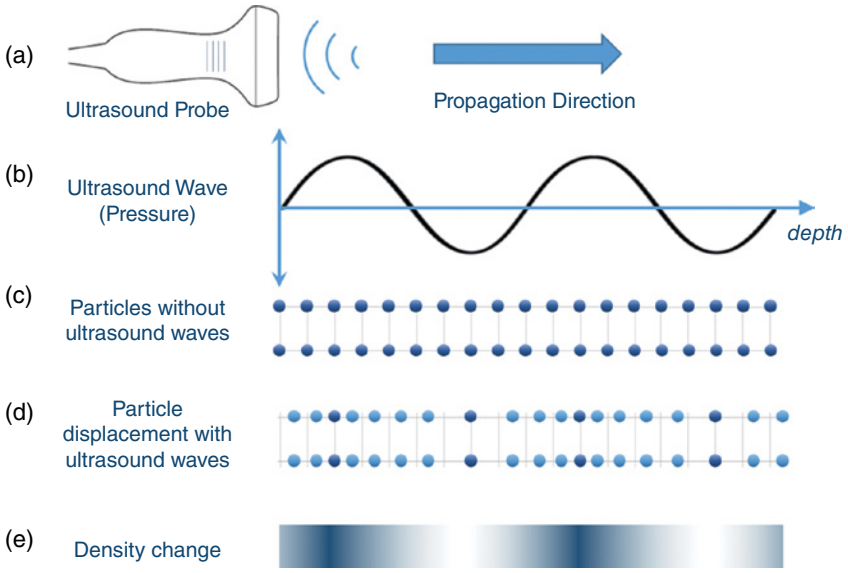

Figure 1.1 (a–e) Longitudinal wave propagation using a simplified physical model depicted graphically. A detailed explanation is in the text above.

Particle velocity should not be confused with the speed of sound. The ultrasound wave travels, while the particles oscillate around their original position. The particle velocity is relatively small in comparison to the speed of sound in the medium.

Speed of Sound, Frequency, and Wavelength

A propagating ultrasound wave can be characterised by its speed, frequency, and wavelength. Similar to other types of waves, the speed of propagation of an ultrasound wave is determined by the medium it is travelling in. Propagation speed is usually referred to as the speed of sound, denoted by '*c*', and it is a function of the density, 'ρ', and stiffness, '*k*', of the medium, as shown in Equation 1.1:

$$c = \sqrt{\frac{k}{\rho}} \tag{1.1}$$

Tissue with low density and high stiffness has a high speed of sound, whereas high density and low stiffness lead to low speed of sound. See Table 1.1 for speed of sound values in different tissue types and materials [2, 3].

In addition to speed of sound, the frequency, '*f*', and the wavelength, 'λ', of the ultrasound wave are crucial parameters for medical ultrasound imaging. The frequency of a wave is the reciprocal of the time duration of a single oscillation cycle of the wave and carries a unit of Hz. The wavelength is the length of a single cycle of the wave and is linked to frequency and speed of sound, as in Equation 1.2:

$$\lambda = \frac{c}{f} \tag{1.2}$$

In short, frequency has the timing information about the wave for a given space, and wavelength has the spatial (relating to physical space) information about the wave at a

Table 1.1 Ultrasound properties of common materials and tissue.

Material	Speed of sound *c* (m/s)	Acoustic impedance *Z* (MRayl)	Density, ρ (10^3 kg/m^3)	Attenuation coefficient at 1 MHz (dB/cm)
Air	330	0.0004	0.0012	1.2
Blood	1570	1.61	1.026	0.2
Lung	697	0.31	0.45	1.6–4.8
Fat	1450	1.38	0.95	0.6
Liver	1550	1.65	1.06	0.9
Muscle	1590	1.70	1.07	1.5–3.5
Bone	4000	7.80	1.95	13
Soft tissue (mean)	1540	1.63	–	0.6
Water	1480	1.48	1	0.002

given time. Ultrasound image resolution is related to frequency/wavelength and is usually better at higher frequencies and shorter wavelengths. At a given ultrasound imaging frequency, the wavelength changes proportionally with the speed of sound. For medical ultrasound imaging, the speed of sound is usually assumed to be constant for the tissue and in order to change the image resolution, one needs to change the imaging frequency. For example, for an average speed of sound in soft tissues of 1540 m/s, the wavelength is 0.77 mm at 2 MHz and 0.154 mm at 10 MHz.

Acoustic Impedance

Acoustic impedance is the effective resistance of a medium to the applied acoustic pressure. For example, the particle velocity in soft tissue will be higher than the particle velocity in bone for the same applied pressure due to the difference in their acoustic impedance (see Table 1.1). The acoustic impedance, '*Z*', of a material is determined by its density and stiffness values, as shown in Equation 1.3:

$$Z = \sqrt{\rho k} \tag{1.3}$$

Physical Processes That Affect Ultrasound Waves

Reflection

When an ultrasound wave travelling through a medium reaches an interface of another medium with a different acoustic impedance, some portion of the ultrasound wave is reflected, as shown in Figures 1.2 and 1.3. The amplitudes of the transmitted and reflected ultrasound waves depend on the difference between the acoustic impedances of both media, see Figure 1.3. This can be formulated as the reflection coefficient, shown in Equation 1.4:

$$R = \frac{Z_2 - Z_1}{Z_2 + Z_1} \tag{1.4}$$

The interfaces with higher reflection coefficients appear brighter on an ultrasound B-mode image, since a large portion of the ultrasound wave is reflected back. Reflection coefficients at some common interfaces are shown in Table 1.2.

It should be remembered that the underlying model for the equation of the reflection coefficient is based on specular reflection, which means a reflection from a perfectly flat surface or an interface.

In reality, the reflection of ultrasound waves can be considered either specular or diffuse (https://radiologykey.com/physics-of-ultrasound-2). When the ultrasound waves encounter a large smooth surface such as bone, the reflected echoes have relatively uniform direction. This is a type of specular reflection, as shown on the left of Figure 1.2. When the ultrasound waves reflect from a soft tissue interface, such as fat–liver, the reflected echoes can propagate towards different directions. This is a type of diffuse reflection, as shown on the right of Figure 1.2.

Refraction

Refraction is the bending of a wave when it enters a medium with a different speed. It is commonly observed with all types of waves. For example, when looked from above, a spoon appears to be bent in a glass full of water. The reason for this is that the light emerging from the water is refracted

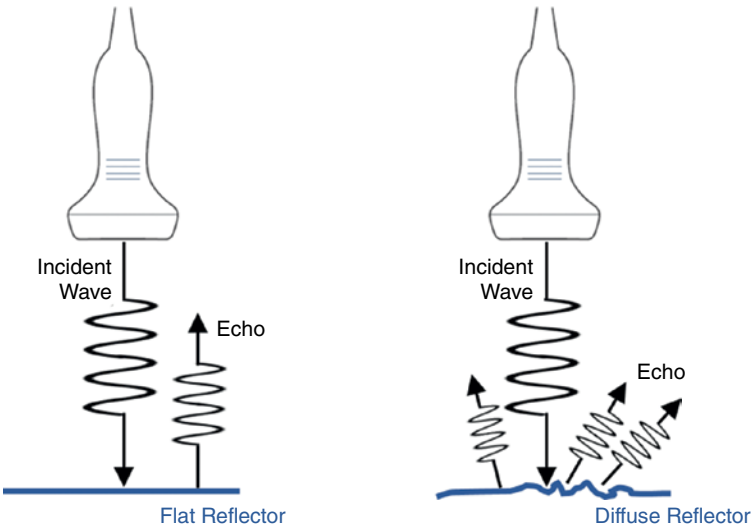

Figure 1.2 Specular (left) and diffuse (right) reflection.

away from the normal, causing the apparent position of the spoon to be displaced from its real position, due to the difference in the speed of light in water and in air.

Refraction of ultrasound waves occurs at boundaries between different types of tissue (different speeds of sound), as shown in Figure 1.3. In ultrasound imaging, this can cause displacement of the target from its true relative position. If the speed of sound is the same in both media, then the transmitted ultrasound wave carries on in the same direction as the incident wave.

Scattering

Human tissue has inhomogeneities. When these inhomogeneities are much smaller than the wavelength, then the ultrasound wave is scattered in many directions, as shown in Figure 1.3. Most of the ultrasound wave travels forward and a certain portion of the wave's energy is redirected in a direction other than the principal direction of propagation. Scattering reduces the amplitude of the initial propagating ultrasound wave, but the lost energy due to scattering is not converted to heat.

Table 1.2 Reflection coefficients at some common interfaces.

Interface	*R*
Liver–air	0.9995
Liver–lung	0.684
Liver–bone	0.651
Liver–fat	0.089
Liver–muscle	0.0149
Liver–blood	0.0123

Scattering plays an important role in blood velocity estimation. Blood cells (e.g. erythrocytes are 6–8 μm) are usually much smaller than ultrasound imaging wavelengths (>100 μm). Therefore, blood does not reflect but scatter the ultrasound waves.

Absorption

Ultrasound waves are pressure waves. They change the local density by compression and rarefaction, where not all adjacent particles move together. When particles are moving towards each other they experience friction. In medical imaging, this friction is caused by the viscoelastic behaviour of human soft tissue, which is effectively the resistance against the motion.

When the local compression generated by the ultrasound waves are resisted by the friction of the soft tissue, heat is generated. In other words, there will be tiny differences in temperature between regions of compression and rarefaction. Tissue will conduct heat from the higher-temperature region to the lower. This overall process will result in a bulk rise in temperature of the tissue due to viscous losses. Consequently, the energy of the travelling ultrasound waves will be lost after propagation.

Attenuation

Attenuation means a reduction in the amplitude of ultrasound waves. In ultrasound imaging, attenuation of the transmitted waves is usually as a result of absorption, but other physical processes also attenuate the waves, such as reflection, refraction, scattering, and diffraction. The amount of attenuation is usually expressed in terms of the attenuation coefficient, as shown in Table 1.1.

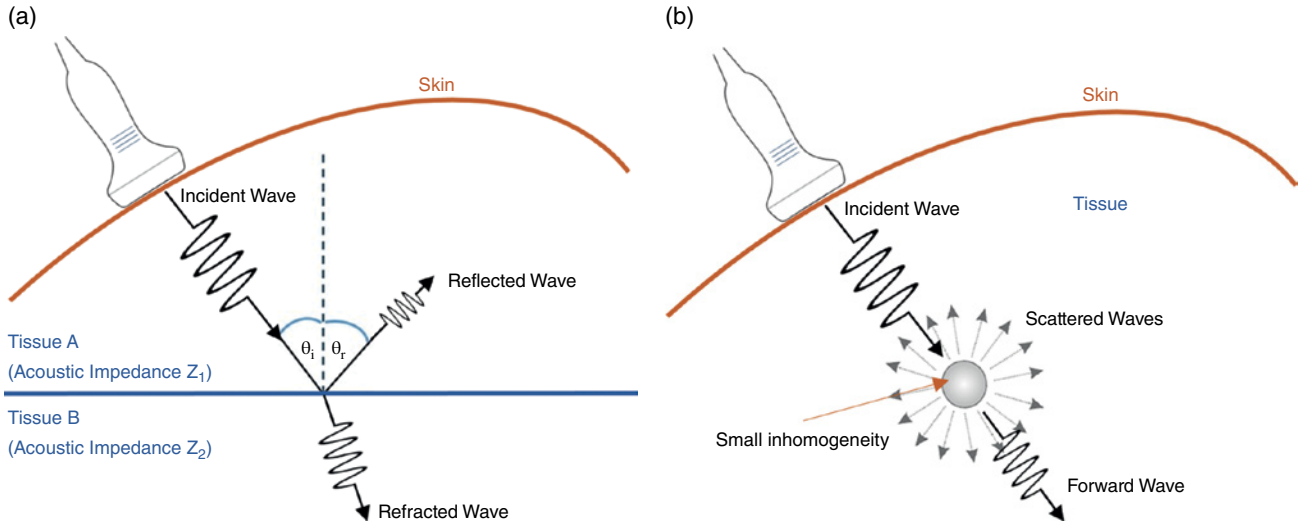

Figure 1.3 (a) Reflected, refracted, and (b) scattered waves.

The most important practical implication of attenuation is that it is hard to achieve good resolution in deep tissue. The image spatial resolution is better at higher ultrasound frequencies. However, the attenuation in tissue is also higher at higher frequencies. Over a given distance, higher-frequency sound waves have more attenuation than lower-frequency waves. This results in a natural trade-off between image resolution (frequency) and imaging depth (penetration). The functionalities to increase the signal amplification with depth in all ultrasound systems, known as time gain compensation (TGC), can, to a limited extent, recover weak signals in deep tissues.

Ultrasound Transducers

A transducer is a device that converts one type of energy into another. An ultrasound transducer generates ultrasound waves by converting electrical energy into mechanical energy. Conversely, an ultrasound transducer can convert mechanical energy into electrical energy. This duality is particularly useful for imaging applications, where the same ultrasound transducer can generate ultrasound waves and also sense the reflected echoes from the human body. Inside all ultrasound imaging probes there are transducer elements that convert electrical signals into ultrasound and, conversely, ultrasonic waves into electrical signals. There are several different methods to fabricate an ultrasound transducer. In this section, we will only explain the piezoelectric materials, which are used in most ultrasound probes.

Piezoelectric Effect

In precise terms, piezoelectric materials work with the principle of piezoelectric effect, which is the induction of an electric charge in response to an applied mechanical strain. The piezoelectric effect explains how ultrasound sensors can detect pressure changes. This effect may be reversed, and the piezoelectric material can be used to generate pressure waves by applying an electric field.

Ultrasound waves can be generated by applying an alternating current (AC) with a frequency closer to the working frequency of the transducer. The AC voltage produces expansions and contractions of the piezoelectric material, which eventually create the compression and rarefaction phases of the ultrasound waves, as shown in Figure 1.4. Usually the displacement on the surface of the piezoelectric material is proportional to the applied voltage. When pressure is applied to the piezoelectric material, it produces voltage proportional to the pressure.

Resonance Frequency

The frequency at which the transducer is most efficient is the resonance frequency. The transducer is also the most sensitive as a receiver at its resonance. If the applied voltage is at the resonance frequency of the transducer, it generates ultrasound waves with the highest amplitude, as shown in Figure 1.5.

The thickness and shape of the piezoelectric material determine the resonance frequency of the ultrasound transducer. The same piezoelectric material can be cut and shaped in different sizes to produce transducers working at different frequencies.

Transducer Bandwidth

Bandwidth is the range of frequencies at which the transducer can operate without significant loss. Piezoelectric materials are resonant systems that work well only at the resonance frequency, but this is not ideal for imaging applications. Imaging applications require a transducer that can work at a range of frequencies. For this reason, manufacturers apply damping to reduce the resonance behaviour.

Figure 1.6 shows the response of a resonant and a highly damped transducer. The undamped transducer has unwanted

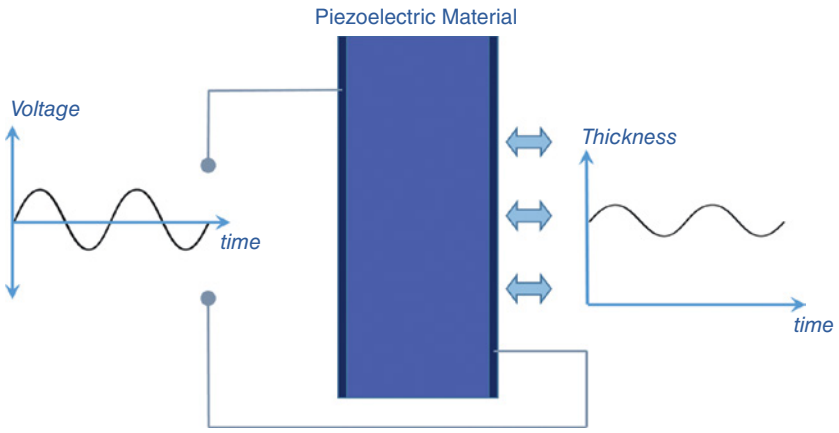

Figure 1.4 Changes in voltage across both sides of the piezoelectric material causes changes in the thickness.

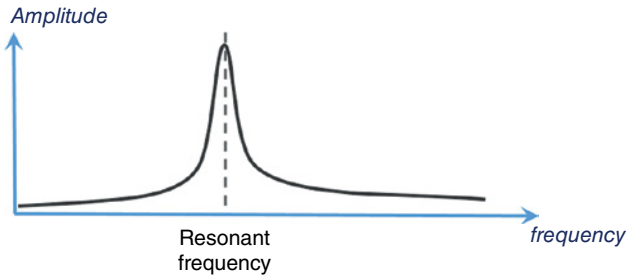

Figure 1.5 Resonance behaviour of piezoelectric ultrasound transducers.

ringing even after the electrical signal stops. This long-duration response of the transducer is not ideal for imaging. A good imaging pulse has a short duration in time, so it can be used to determine objects close to each other. A short pulse contains a range of frequencies and is better accommodated by a transducer with wide bandwidth, such as the damped transducer shown in Figure 1.6.

Single-Element Transducer

Single-element ultrasound transducers are fabricated by using one plate of piezoelectric material, as illustrated in Figure 1.7. A thin plate of piezoelectric material (shown in dark blue) is coated on both sides with a conductive layer, forming electrodes. Both electrodes are bonded to electrical leads that are connected to an external system to transmit or receive ultrasound waves. The front electrode is usually connected to the metallic case of the transducer and the electrical ground for safety. The back electrode is the electrically active lead. In order to transmit an ultrasound wave, an oscillating voltage is applied to the electrodes. A matching layer is specifically designed for a target application, such as imaging the human body, and it increases the coupling efficiency of the transducer to the body. An acoustic lens may be placed in front of the matching layer to create a weak focal zone. This is particularly useful for small (small in comparison to the operating wavelength) transducers that diverge ultrasound waves outside the imaging region. The backing layer is specifically designed to absorb unwanted internal reverberations. It effectively dampens the resonance behaviour of the piezoelectric material and increases its bandwidth.

Imaging with a Single Element

A single-element transducer can act as a transmitter and also as a receiver. This makes it possible to measure the elapsed time between the transmission of an ultrasound pulse and the reception of its echo from a reflecting or scattering target. If the speed of sound in the medium is known, then the distance to the source of the echo can be

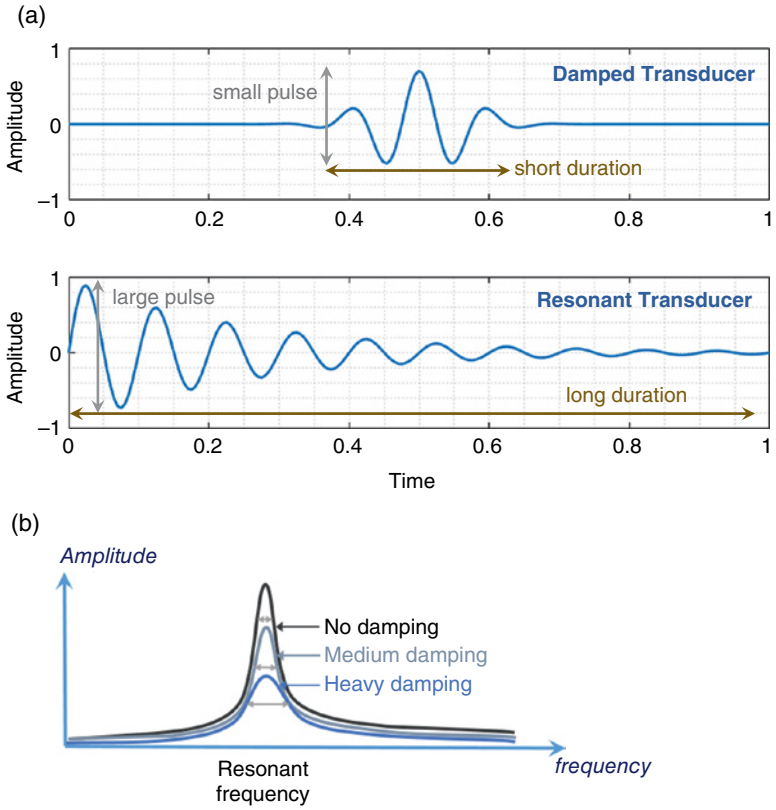

Figure 1.6 Response of a highly resonant transducer and damped transducer to a short electrical pulse. (a) Transducer response measured as a function of time. (b) The corresponding frequency response.

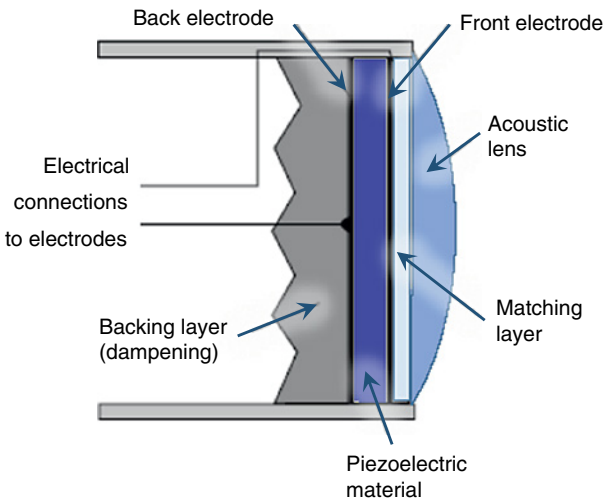

Figure 1.7 An ultrasound transducer's internal architecture.

calculated. After a single measurement, the depth and the amplitude of the echo, which are related to the ultrasonic properties of the target, can be calculated.

This measurement method is usually called a pulse–echo method or an A-scan. It is possible to generate an image by moving the transducer element and performing several A-scan measurements. However, this is not practical for imaging, since it requires a mechanical motion and knowledge of the exact transducer location in order to precisely combine the A-scan measurements. The mechanical scanning method is slower than the electronic scanning method, which will be explained in the next section.

Array Transducers and Transmit Beamforming

Most clinical ultrasound imaging probes consist of an array of transducer elements. Arrays provide flexibility as the transmitted ultrasound beam can be changed on the fly, which is not possible with solid apertures or single-element transducers. The array transducers usually have hundreds of elements with a single front electrode connecting all elements together to the electrical ground. This is important for safety and also reduces fabrication complexity. Each element has individual electrodes at the rear, and these are connected to the imaging system with a separate cable, as shown in Figure 1.8. The ultrasound system can control each element individually during the transmit and receive cycles. By controlling the timing of transmission in each element, the ultrasound beam can be focused or steered electronically at different depths and directions in so-called transmit beamforming.

Line-by-Line Scan

The most common ultrasound imaging method is line-by-line image formation. In this method, the ultrasound energy is focused into a long and narrow region, as illustrated by the arrows in Figure 1.9 for different type of imaging probes. The received echoes from each transmission form a single line in the ultrasound image. After completing a transmit–receive sequence, the scan line is moved to the next position. The repositioning of the scan line is achieved electronically by controlling the timing of transducer elements. Electronically scanned arrays do not have any moving parts compared to mechanically scanned solid apertures, which are slow and require maintenance. It should be noted that the 'image line' is in reality a 3D volume, as shown in Figure 1.9d, narrower at the focal plane and wider elsewhere.

Ultrasound Image Formation

The transmitted ultrasound waves propagate through tissue and are reflected and scattered from tissue boundaries and small inhomogeneities wherever there is an acoustic impedance mismatch. A portion of these reflected and scattered ultrasound waves travels back to the transducer and is then converted to electrical signals by the transducer elements. Each element on the transducer provides a distinct electrical signal where the timing of each signal accommodates the distance information. Signals from each element are normally called channel signal. All channel

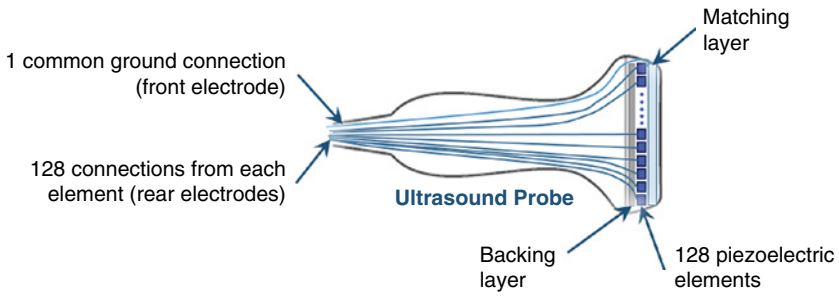

Figure 1.8 Schematic of an array transducer.

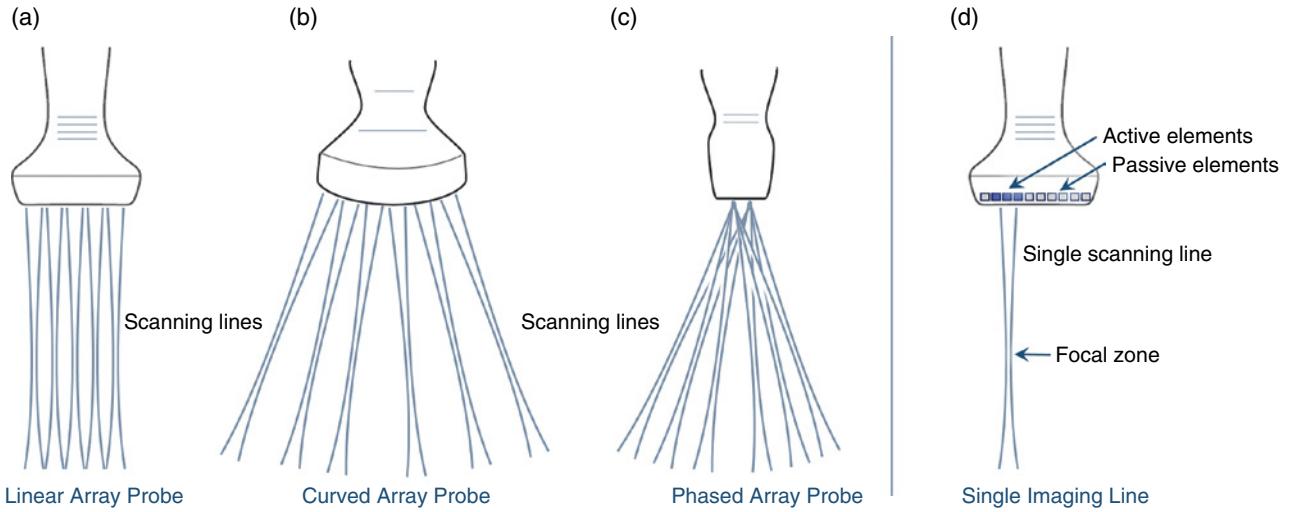

Figure 1.9 The line-by-line scanning approach is illustrated for different types of ultrasound probes used for liver scans. (a) Linear array. (b) Curvilinear array. (c) Phased array. (d) An imaging line.

signals are processed to reconstruct the images in different imaging modes with three main steps, pre-processing to amplify signals and remove noises, receive beamforming to reconstruct the image, and post-processing to enhance the image quality.

Pre-processing and Receive Beamforming

Pre-processing

Pre-processing is to enhance the received signals and remove noises for each channel signal before the receive beamforming. The first step is to amplify the received channel signals, as their amplitudes are generally too small to be processed directly by a beamformer. Besides the signal pre-amplifiers, to which users do not have access, there are two types of amplifiers that can be controlled by users: an overall amplifier and a TGC (Figure 1.10). The overall amplifier enhances the received signals as a whole, regardless of where these signals are originating from, while the TGC amplifies the signals based on the arrival time to have later-arriving signals from deeper regions being amplified more as they are more attenuated. Although these user-controlled amplifiers are to enhance the received signals, they also amplify the noise. To ensure a sufficient signal-to-noise ratio (SNR), a certain level of transmission power is required.

Figure 1.10 The typical time gain compensation (TGC) slide controls for different gains at different depths.

Band pass and other filters may also be used after the amplifications to remove some electrical noise in the signals. Signals received at each channel are analogue signals, which vary continuously. The beamforming and all post-processing in modern scanners are done in digital form. Therefore, analogue-to-digital conversion (ADC) is always required for digital processing.

Delay-and-Sum Receive Beamforming

In receive beamforming, the echoes received from all transducer elements are realigned in time through pre-determined time delays, so that only the echoes originating from the same spatial locations (pixels) are summed. In clinical ultrasound scanners, the images in all modes are typically formed with line-by-line transmitting and receiving, so signals from each transducer element are realigned to focus at specified depth(s) for each scanning line after the ADC. The realignment is done by compensating for the arriving delay time, which is determined by the path length between the specified depth and the individual elements, as shown in Figure 1.11. Then the realigned signals corresponding to a certain spatial location (pixel) are summed. This beamforming method is called delay-and-sum (DAS). In order for every pixel, or depth along the scan line, to be in focus in the reconstructed image, the delays to arrival time in DAS need to be adjusted dynamically to achieve

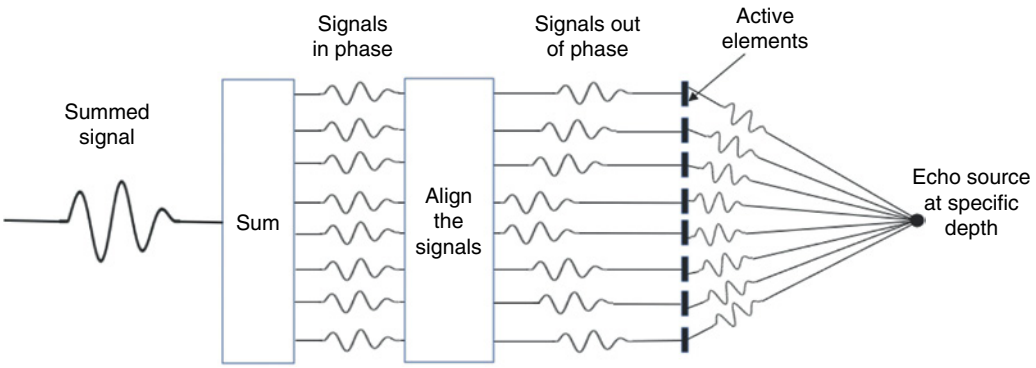

Figure 1.11 The delay-and-sum receive beamforming method for obtaining the in-phase summation of signals from individual active elements at a specific focusing depth. 'Dynamic focusing' means the delays need to be calculated for multiple depths.

continuous advancement of the focusing depth and have what it is called 'dynamic focusing in reception'.

Most ultrasound imaging modes, including B-mode ultrasound, Doppler ultrasound, and elastography, need to have the pre-processing and line-by-line receive beamforming procedure before the image display. The differences among those imaging modes start from post-processing after line-by-line beamforming, which will be explained in the following sections.

B-Mode Ultrasound

B-mode ultrasound in this chapter (B stands for brightness) refers to virtualising the tissue structures based on the brightness of received signals. According to the frequency components of the received signals selected for B-mode imaging, there is fundamental frequency imaging or harmonic imaging.

When an acoustic wave propagates in the human body, in addition to the attenuation of its amplitude, its initial shape and frequency compositions can also be gradually altered by the tissue as it propagates, a phenomenon called non-linear propagation. This is due to the fact that the local tissue density does not respond entirely proportionally to the local ultrasound compression or rarefaction pressure, especially at high acoustic pressures. Consequently, the propagating wave, as well as the received signals, not only has the same frequency components as the transmitted pulse (called fundamental frequency), but also harmonic frequencies, which are multiples of the transmitted frequencies. This distortion tends to occur when the transmitted pulse has high pressure or when there are ultrasound contrast media along the propagation path.

The different frequency components of the received signals have different characteristics, and the choice of which component to use forms the basis of the two imaging approaches, fundamental frequency imaging and harmonic imaging. Image reconstruction in both categories is to be explained in this section.

Fundamental Frequency B-Mode Imaging

This imaging approach assumes that the higher harmonic frequencies in the received signals can be discarded and only considers the fundamental frequency components. After the DAS beamforming, the summed signal is still in the radio frequency (RF) domain, oscillating at the transmitted frequency when non-linear propagation is ignored. This RF signal can be described as a modulated sinusoidal signal, which has the amplitude and phase information. In B-mode imaging, it is the amplitude information that determines the brightness of the image; the phase information is normally discarded. A procedure called amplitude demodulation is applied to extract this envelope information by removing the oscillating carrier frequency, as shown in Figure 1.12. Envelopes from each scanning line will be used to form a two-dimensional B-mode image.

Harmonic Imaging

In harmonic imaging, signals at the transmitted fundamental frequency are removed from the beamformed RF signal, and only the harmonic components are selected for extracting the envelope information and forming B-mode images. This is typically done by filtering out the fundamental components with a bandpass filter. One of the advantages of using harmonic components is that the beam width in the lateral direction is narrower than that of the fundamental components (Figure 1.13), which will give better lateral resolution, as explained in the next section. After removing the fundamental frequency components, amplitude demodulation is also needed to extract envelopes from harmonic components in each scanning line to form the 2D image.

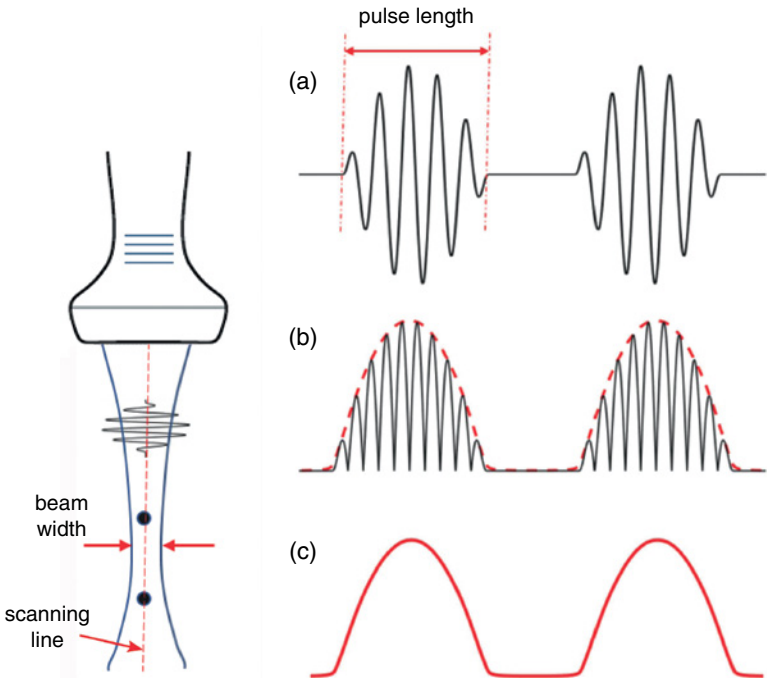

Figure 1.12 A pulsed ultrasound beam to image two point sources along one scanning line shown on the left. (a) The beamformed radio frequency signal. (b) Amplitude modulation applied to get the envelope of the two point sources. (c) The extracted envelope on this scanning line for the image display.

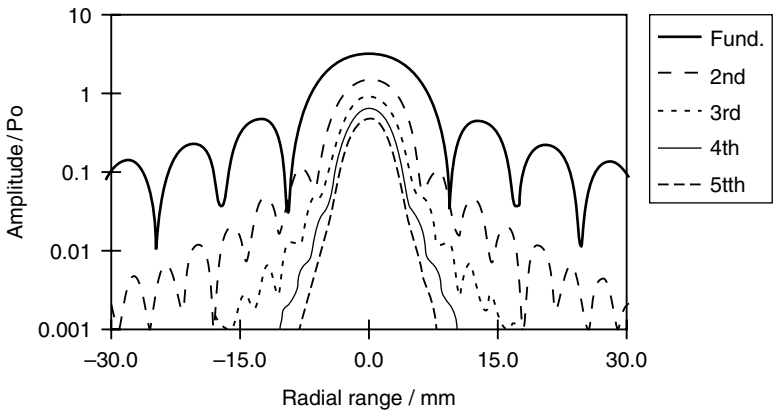

Figure 1.13 Computed harmonic beam profiles in the focal plane of a 2.25 MHz transducer, where lateral resolution is much improved with harmonic imaging. *Source:* Reproduced by permission from Duck, F.A., Baker, A.C., Starritt, H.C. (eds) (1998) *Ultrasound in Medicine*, Boca Raton, FL: CRC Press.

Image Resolutions

When evaluating the performance of an imaging system, the user should consider three different resolutions: temporal resolution, spatial resolution, and contrast resolution. The *temporal resolution* is to measure how many image frames can be reconstructed per second (fps). High temporal resolution is required to capture the fast-moving objects in the tissue, such as the moving heart and blood flow.

Spatial resolution is to evaluate the ability of an imaging system to distinguish the two closest points in a 3D object space. It includes the spatial resolution in the axial direction, lateral direction, and elevational direction in the ultrasound imaging coordinates (Figure 1.14). Spatial resolution in the axial direction is determined by the length of the transmitted pulse (Figure 1.12), which in turn is determined by the central frequency of the transmission and the bandwidth of the system. In the lateral direction, the resolution is related to the lateral beam width (Figure 1.12) and depends on the size of the transducer aperture and the imaging depth; it is typically between one and two wavelengths of the transmitted waves. In the elevational direction, the resolution is determined by the thickness of the scan plane, also called slice thickness, which varies with depth. Most transducers have a fixed focusing depth in the elevational direction, achieved by a cylindrical acoustic lens attached to the transducer face. Even with the lens focusing, the slice

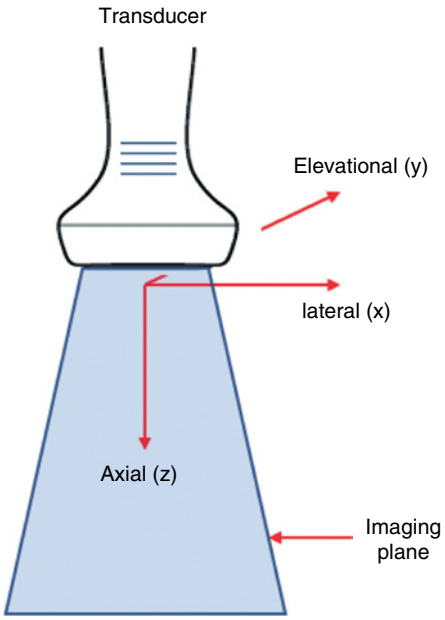

Figure 1.14 The conventional coordinate system in an ultrasound imaging system.

thickness is generally larger than the beam width in the lateral direction.

Contrast resolution defines the ability to differentiate an area of tissue from its surroundings. This ability is important in ultrasound diagnosis, since it can help identify different organs and monitor pathological change. Compared to magnetic resonance imaging (MRI), ultrasound imaging has relatively less contrast resolution due to the similar echogenicity of different soft tissues in the body.

Image Display

Before displaying the image on the screen, it is necessary to compress the signals into a certain dynamic range. This is because the reflected intensity from different tissues spreads over a large range. If all these intensities were displayed on the screen in a linear scale, the weak echoes scattered from most soft tissues would be dark in the image, and only the echoes from large surfaces/interfaces would stand out. To address this issue, the large-range intensity values of echoes are compressed to simultaneously display strong echoes from, for instance, organ interfaces and weak signals from within soft tissues. This compression process is normally a non-linear procedure such as logarithm compression, which amplifies the weak echoes more than it does the large echoes. In commercial ultrasound scanners, the non-linear compression curve can be adjusted to have a different dynamic range for the final image display.

After compression, the image can be displayed on the screen for diagnosis. From ultrasound transmission to final display the whole process can be in real time. Modern commercial systems may also use some advanced filters to reduce the speckle effect in the image or further smooth the image for an improved visual display.

Doppler Ultrasound

Medical Doppler ultrasound uses ultrasonic waves for measuring blood flow in the cardiovascular system as well as tissue motion. It has been widely used in clinical practice; its high temporal resolution and real-time imaging make it a unique modality for blood flow measurements. Over the past 50 years, most Doppler systems may be categorised as the continuous wave (CW) Doppler system and the pulsed wave (PW) Doppler system. The two types of system have their own advantages, but PW systems are more commonly used in modern scanners. In Doppler ultrasound, ultrasonic waves are transmitted through a transducer and are scattered by the moving red blood cells and then received by the same aperture (in a PW system) or a separate one (in a CW system) for extracting the blood flow velocities with signal processing algorithms. Both CW and PW systems are based on the Doppler effect for the estimation of blood flow or tissue motion velocities.

Doppler Effect

The Doppler effect refers to the shift in the observed frequency of a wave as a result of motion from the wave source or from the observer. In ultrasound flow imaging the ultrasound transducer, which is fixed in one position, transmits a sound wave at a frequency of f_t and this sound wave will hit blood cells; meanwhile the blood cells are moving at a velocity of v. The frequency f_r of the sound wave scattered by blood cells and received by the transducer will have the relation shown in Equation 1.5:

$$f_d = f_t \cdot \frac{2v}{c} \tag{1.5}$$

If the blood flow is static, the received wave and transmitted wave have the same frequency, so the Doppler frequency shift will be zero (Figure 1.15). The received wave will have a higher frequency than the transmitted wave if the blood cells are moving towards the transducer, producing a positive Doppler frequency shift, and vice versa. When there is an angle θ between the direction of the moving blood cells and the ultrasonic sound wave beam direction, a triangular relation needs to be considered, giving the final Doppler frequency in Equation 1.6:

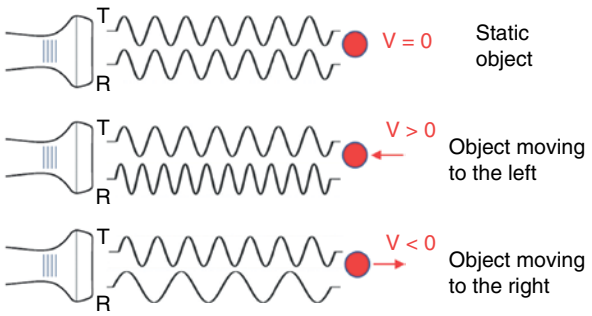

Figure 1.15 Doppler effect occurring due to blood cell motion.

$$f_d = f_t \cdot \frac{2v\cos(\theta)}{c} \tag{1.6}$$

From this relation, it is clear that the angle between the transmitted sound beam and the flow must be smaller than 90° to generate a shift in frequency. To avoid a 90° beam incident, the transmitted beam sometimes is intentionally steered to have a small angle to the vessel wall. From Equation 1.6, it can also be seen that a typical blood velocity of 1 m/s will only produce a Doppler frequency of about 6.4 kHz when the transmitted frequency is 5 MHz, which is a very small fraction of the transmitted frequency (about 0.1%).

Flow Measurement and Imaging Using Doppler

There are different types of clinical Doppler techniques, depending on the way ultrasound waves are transmitted and echo data processed. CW Doppler transmits a constant wave with one transducer (or a group of transducer elements) and receives with another, while PW Doppler uses the same transducer element(s) for both transmission and reception.

Once the echo signals are received they need to be processed to extract the blood flow information. While some processing is different between the Doppler techniques, the processing steps in common include demodulation and tissue clutter filtering. The demodulation is to remove the transmitted carrier frequency in the RF signal so that only the frequency changes caused by motions are kept. This procedure is similar to that in B-mode imaging, but in Doppler imaging the phase information also needs to be extracted. In practice, motions of the tissue within the path of the ultrasound beam, which could be introduced by pulsatile flow in blood vessels and the pumping heart or breathing, also generate Doppler signals together with the moving blood. Doppler signals caused by tissue motions need to be removed to have an unbiased estimation of blood flow velocities. Typically, signals from moving tissues have about 40 dB (100 times) higher amplitude than signals from moving blood cells. In contrast, the Doppler frequency components arising from tissue motions are lower than those from moving blood cells, as blood cells can move at a velocity as high as a few metres per second (up to ~5 m/s), while even the myocardium and the heart valves normally move at a speed of less than 0.1 m/s. The differences in frequency between Doppler signals from moving blood cells and moving tissues make it possible to separate them. Clutter in Doppler ultrasound refers to tissue signals that interfere with the detection of moving blood cells, and can be filtered out by a high-pass filter in the frequency domain. This is also called a 'wall filter', although it is not limited to removing signals coming from the moving vessel walls. The hypothesis is that clutter has lower-frequency components, so a high-pass filter in the frequency domain can remove the clutter by choosing the right frequency threshold. This frequency filter will remove any signals below that threshold, meaning signals from slow-moving blood cells are also cut off altogether. In modern ultrasound scanners, the cut-off threshold can be adjusted by the user depending on different clinical applications.

Continuous Wave Doppler System

In a CW system, ultrasound waves are continuously transmitted by one set of elements in the transducer and received continuously by a separate set of elements, as shown in Figure 1.16. The biggest disadvantage of the CW system is that it does not provide specific depth information about where the blood flow is being measured. The measurements are made within the whole sensitive region, which is the overlap region of the transmitted and received beams (Figure 1.16), and depends on the positions of transmitting and receiving apertures and the transmitting beam steering angle. The CW system is still commonly used in clinical practice, as it has the advantage of being able to measure blood flow with very high velocity.

After demodulation and clutter filtering, what remains are the Doppler signals arising from the moving blood cells from within the sensitive region, as shown in Figure 1.16. The next step is to estimate the frequency components, which are related to the blood flow velocities. In the CW

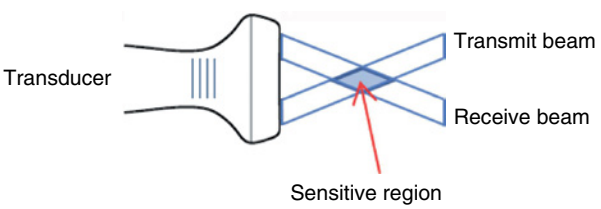

Figure 1.16 Continuous wave Doppler system.

system, the estimator used is called fast Fourier transform (FFT), which takes a segment of 5–20 ms of the Doppler signal samples to generate one frequency spectrum. Frequency components in this spectrum are converted into velocities according to Equation 1.6. A series of FFTs need to be done to process all the received signals for a real-time display.

The flow velocity display in a CW system is called a sonogram, as shown in Figure 1.17. In a sonogram, the horizontal axis represents the time and the estimated velocity is shown along the vertical axis. Each column of the sonogram is one spectrum estimated by the FFT estimator. The brightness of each pixel in the sonogram relates to the number of blood cells travelling at a particular velocity within the sensitive region. The horizontal baseline corresponds to zero velocity, which is the defining line for positive and negative flow with regard to the transducer. Normally, it is designed to have positive velocity (blood moving towards the transducer) locate above this baseline and negative velocity (blood moving away from the transducer) below the baseline. This convention can be changed by the operator in the scanner's settings. The Doppler shift frequency in medical imaging is generally within the audible range so that it can also be played by a speaker for clinicians to listen to.

Pulsed Wave Doppler System

In a PW system, pulsed waves are transmitted and the same transducer can be used both for transmission and reception. A PW system is shown in Figure 1.18.

The advantage of PW Doppler is that both the depth and size of the region of interest for acquiring Doppler signals (also called sample volume or range gate) are known, and can be adjusted manually by the operator on the screen of the scanner in real time. The transmitting time of each pulse can be used as a reference to retrieve the depth information of the received signal by assuming that the speed of sound in tissue is constant and known. There are three different Doppler imaging modes that are based on the PW system: spectral Doppler, colour Doppler, and power Doppler.

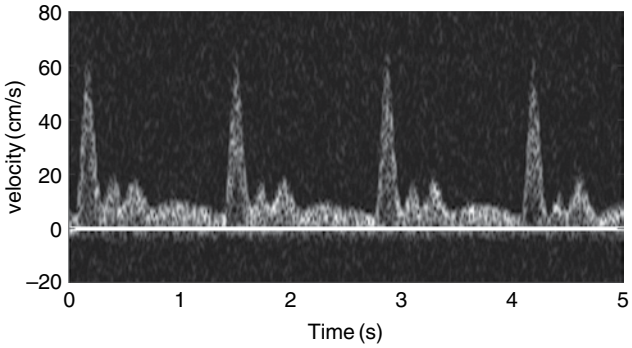

Figure 1.17 A sonogram of continuous wave Doppler and pulsed wave spectral Doppler.

Spectral Doppler

Spectral Doppler in the PW system is very similar to CW Doppler in terms of signal processing in demodulation, clutter filtering, frequency estimation, and display, making them indistinguishable to some degree. The only difference is that the signal is not received continuously but in a pulsed way. It is also this difference that allows the operator to adjust the sensitive region (depth and length of the range gate) in PW spectral Doppler, and a velocity sonogram can be displayed in real time. The ability to have these real-time adjustments and the availability of quantitative velocity information makes spectral Doppler one of the most common Doppler techniques in clinical practice. The disadvantage of a PW system compared to a CW system is that it has an aliasing problem when the blood flow to be measured is moving at high speed. This issue will be explained later.

In PW spectral Doppler, samples within the echoes corresponding to consecutive pulses originating from the chosen depth are combined in sequence to form a sampled Doppler signal. Then the same processing as in CW Doppler is applied to generate spectra for sonogram display (Figure 1.17). The chosen depth in the sampling procedure corresponds to a fixed spatial position, and it is adjustable by the user.

The sampling procedure in pulsed signals could cause aliasing when the blood flow is moving at high speed. This is similar to that in sampling theory, where a higher sampling rate is required to keep the higher-frequency components in a signal (the Nyquist theorem). In the PW system, each received pulse provides the Doppler signal with one sample. Blood flow moving at high speed will generate high-frequency components in the Doppler signal, as explained in Equation 1.5, meaning that a higher sampling frequency is required to avoid aliasing. The sampling rate in the PW system is the pulse repetition frequency (PRF) of the system, which is limited by the speed of sound for a specific imaging depth. According to the Nyquist rule, the PRF must be at least twice as high as the maximum Doppler shift frequency component.

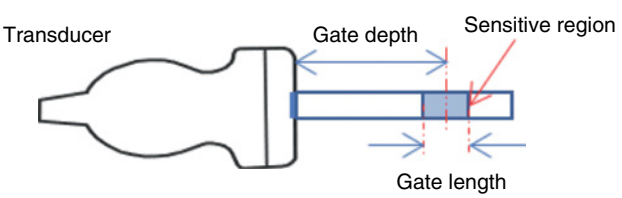

Figure 1.18 Pulsed wave spectral Doppler system.

According to Equation 1.5, the Doppler shift frequency is 6.4 kHz when the blood cells move at 1 m/s and the transmitted frequency is 5 MHz, so the PRF must be more than 12.8 kHz. It is difficult to achieve such a high PRF for a PW system, as it is always interleaved with B-mode and/or colour Doppler to obtain a duplex or triplex mode in clinical practice. One way to mitigate this issue is to use a lower transmitted frequency to have a proportionally lower Doppler shift frequency under the same blood velocity. This is the reason the transmitted frequency in PW spectral Doppler is normally lower than 5 MHz, to avoid aliasing for high-speed blood flow applications. Another way is to adjust the baseline in the sonogram to give a larger range in the direction (positive or negative) where the flow velocity is larger.

Colour Doppler

Spectral Doppler can only measure the blood flow velocities from within a range gate. It is not able to cover a larger region of interest, although it allows the user to adjust the location of the range gate. Colour Doppler is for a 2D blood velocity visualisation, and it always works together with B-mode imaging to have the colour-coded velocity map superimposed on the B-mode image. In most modern scanners, it is also possible to combine anatomical B-mode image, spectral Doppler sonogram, and colour-coded velocity map into one image on the scanner's screen, as shown in Figure 1.19. This is possible because all these three modes are based on pulsed wave transmitting and receiving, so interleaving strategies can be designed to allow them to work in a dedicated sequence.

In CW Doppler and spectral Doppler, there is only one received ultrasound beam to estimate the flow velocity along one scanning line. In colour Doppler, a series of beams sweeping along the transducer's element array are transmitted and received, forming an 2D region of interest in a similar way as is done in standard B-mode imaging. Each of these beams is transmitted and received in the same way as in spectral Doppler, but it contains multiple adjacent range gates along its scanning line rather than only one range gate. Within each range rate, it is the mean velocity component (instead of a spectrum in CW or PW Doppler) along the beam direction that is being estimated in colour Doppler. The same demodulation and clutter filtering are done here as in CW Doppler and spectral Doppler. In principle, the mean velocity in each range gate can also be derived by FFT of the demodulated Doppler signal to the frequency domain, followed by extracting the mean frequency shift in the spectrum. However, this is not how it is done in most commercial scanners, since this method would take too much time to have a 2D mean velocity map in real time.

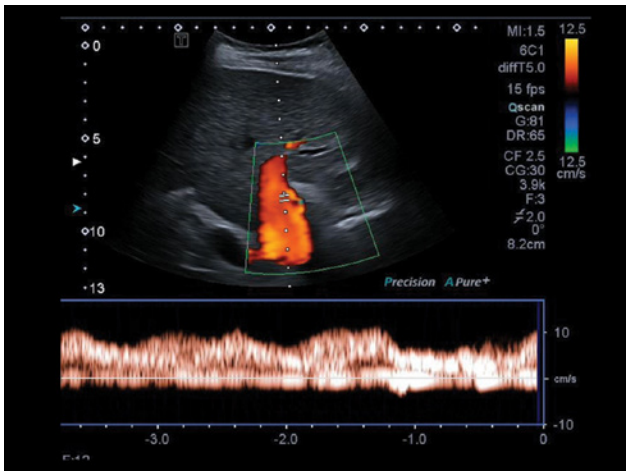

Figure 1.19 B-mode, spectral Doppler, and colour Doppler in a triplex mode assessing flow in the portal vein.

Instead, an autocorrelation estimator is adopted in colour Doppler, which can directly obtain the mean flow velocity through estimating the mean 'phase shift' at each location with an ensemble of consecutive received echoes. The number of pulses required along each scanning line is important for the estimation. Typically over 10 pulses per scan line are necessary for an acceptable mean velocity estimation, especially for low-level velocities. This means the frame rate in colour Doppler will be reduced by ≥10 times compared with B-mode imaging. The compromise between the frame rate and the quality of velocity estimation in colour Doppler presents challenges in dealing with fast flow while maintaining the real-time imaging frame rate. Two measures can be taken to increase the frame rate in colour Doppler without compromising velocity estimation. The first one is to restrict the imaging field of view by defining a colour box, and only estimating the colour-coded velocities within the colour box. The size and position of this colour box can be adjusted by the user. In this way, the number of scanning lines is reduced to only fill up the colour box, and each scanning line does not need to cover the whole depth on the B-mode image. The second method could be to have a lower line density, meaning less time needed for each imaging frame. A typical colour box is given in Figure 1.19. Normally in colour Doppler, red is used to represent the blood flow moving towards the transducer and blue for the flow moving in the opposite direction, but this can be changed by the user in the settings.

Power Doppler

Most of the basics discussed in colour Doppler remain the same in power Doppler, except that power Doppler displays the power of the blood flow signals, a measure of the amount of blood cells, instead of the mean flow velocity of the blood cells as in colour Doppler. The calculated signal power is proportional to the square of the amplitude of the demodulated and clutter-filtered Doppler signal, and this

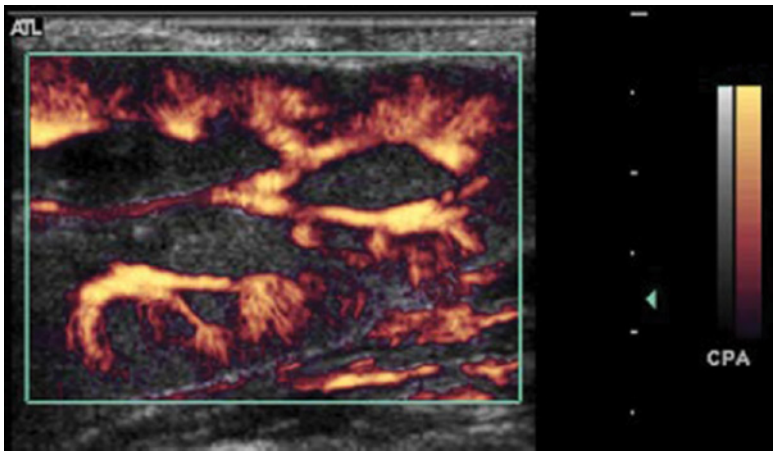

Figure 1.20 A typical colour-coded box estimated from power Doppler superimposed on a B-mode image. *Source:* Reproduced by permission from Hoskins, P.R., Martin, M.K., Thrush, T.A. (2019) *Diagnostic Ultrasound: Physics and Equipment*, London: Taylor & Francis.

power information can also be estimated by the autocorrelation estimator used in colour Doppler.

An example of power Doppler is shown in Figure 1.20, where the colour relates to the local density of moving blood cells. Since there is no directional information about the moving blood cells in the signal power, the conventional power Doppler method does not contain information on the blood flow direction. The instrument settings for displaying colour Doppler and power Doppler are usually the same.

Compared to colour Doppler, which can image the flow dynamics, power Doppler does not generate velocity information and could be optimised, for instance through temporal averaging, to have better sensitivity for visualising vascular morphology. Temporal averaging can reduce the noise level in the image, making it possible to distinguish small vessels. Flow direction information can also be introduced to power Doppler, for example by incorporating flow direction estimation from colour Doppler.

Challenges with Doppler Flow Imaging

While tissue signals can be suppressed and blood flow can be specifically imaged using Doppler techniques, there are significant limitations. Doppler techniques depend on the echoes from blood cells that are very weak, more than an order of magnitude weaker than surrounding tissues. Therefore, Doppler signals are usually noisy, and it is difficult to detect the signal from small vessels such as small arterioles, venules, and capillaries.

Microbubble Contrast Agents

Microbubble contrast agents are micro-sized gas bubbles. They are sufficiently small that after being introduced, typically through intravenous injection, they are able to cross the capillary bed of the pulmonary circulation. At the same time, these bubbles are big enough that they do not cross the vascular endothelium, making them true intravascular agents compared to the MRI or CT agents, which often can leak out of the vasculature. In order to prevent the bubbles from rapidly dissolving and/or agglomerating, they are stabilised by a coating of a biocompatible surfactant or polymer (see Figure 1.21), most commonly phospholipids or proteins. This coating both lowers the interfacial tension at the bubble surface and also provides a barrier to gas diffusion.

Despite being similar in size to red blood cells, bubbles are much more efficient scatterers of ultrasound owing to the fact that they are filled with gas. The gas presents a significant interface with acoustic impedance mismatch where strong scattering occurs. Furthermore, due to the gas being highly compressible, bubbles undergo volumetric oscillations in response to the oscillatory ultrasound pressure changes, and can absorb and reradiate the incident sound efficiently rather than merely acting as passive reflectors. This makes bubbles highly sensitive agents, and it has been well demonstrated that with the appropriate imaging parameters, a single micro-sized bubble can be detected by an ultrasound scanner. Following injection, the bubbles circulate throughout the vascular space and greatly increase the amplitude of the scattered signals from within the blood, making the blood flow from very small vessels and even capillaries detectable.

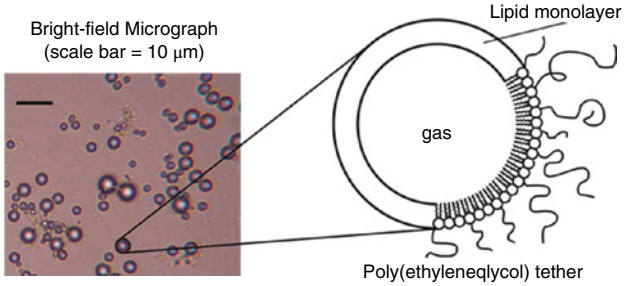

Figure 1.21 Microbubble contrast agents. Left: bright-field micrograph of a microbubble population; right: the compositions of a typical microbubble contrast agent.

While Doppler signals can be significantly enhanced by microbubbles, imaging small vessels presents an extra challenge, as the flow velocity in such small vessels is low. Doppler techniques rely on the difference in velocity between flow and tissue to remove the tissue clutter from Doppler signals. Within small vessels where flow can be as low as millimetres per second, it is difficult to distinguish flow from tissue clutter based only on Doppler velocity estimation, particularly when tissue is also in motion.

Non-linear Behaviour of Microbubbles

Microbubbles' behaviour under ultrasound heavily depends on the amplitude of the ultrasound. The transmit amplitude of the ultrasound is usually indicated by the mechanical index (MI) displayed on the scanner screen. MI is a measure of the potential for mechanical bioeffects (cavitation) in tissue owing to ultrasound exposure, and is defined as the peak negative ultrasound pressure in kPa divided by the square root of the ultrasound frequency in MHz. At a very low MI, the microbubbles undergo volumetric oscillation with radius change approximately proportional to the ultrasound pressure; that is, the oscillation is linear. As the MI increases some microbubbles starts to oscillate, with greater radius changes that are no longer proportional to the ultrasound pressure changes. This is a non-linear process and higher harmonic signals with frequencies at multiples of the fundamental ultrasound frequency can be generated by the microbubble oscillation, even at an MI as low as 0.05. When the MI goes above a certain level (typically between 0.1 and 0.3 depending on the bubble types and ultrasound frequency), some microbubbles start to be destroyed by ultrasound, resulting in reduced contrast enhancement.

Bubble Imaging: High Mechanical Index Destructive Imaging versus Low Mechanical Index Bubble-Specific Imaging

At a high MI microbubbles are easily destroyed and hence the contrast enhancement only happens in the very first few imaging frames with a 'flash' in image intensity. This is due to the fact that the microbubbles can generate strong echo signals while being destroyed. However, in order to maintain the contrast enhancement, lower MIs have to be used. Currently in clinical practice, depending on the different parts of the body and the agent type, the MI typically ranges from 0.04 to 0.3.

While microbubbles can significantly enhance the signal from within the blood, the amplitude of the echoes from within the blood is still at a similar level to those of surrounding tissues. Doppler can be used to separate blood flow from the tissue depending on the motion (blood flow). However, there is a lower limit in flow velocity for Doppler detection: when the flow velocity is close to tissue motion (due to the heart or breathing), blood flow can no longer be separated from surrounding tissue using Doppler, even when microbubble contrast agents are present.

Bubble-specific imaging techniques have been developed to separate the bubble echoes from tissue echoes based on the harmonic signals in the echoes. At a low MI, tissue generally does not produce higher harmonic signals and only bubbles do. Such harmonic signals specifically from microbubbles can be separated from tissue by using multiple pulse transmissions such as pulse inversion or amplitude modulation, as shown in Figure 1.22. In pulse inversion, positive pulse and its inverse are transmitted, and the corresponding received pulses can be summed to form a signal for the image reconstruction. The summed signal will only contain the harmonic components that from tissue are caused by microbubbles even when they are stationary, as fundamental components from tissue are cancelled out due to the linearity. In amplitude modulation, two pulses are transmitted at different levels of amplitude (normally the amplitude of one pulse is doubled, as shown in Figure 1.13); received echo 1 is first multiplied by a factor of two and subtracted from echo 2 to remove the fundamental components from tissue.

Quantification Based on Contrast-Enhanced Ultrasound

In contrast-enhanced ultrasound (CEUS), a time series of contrast-specific images can be obtained, and the tissue

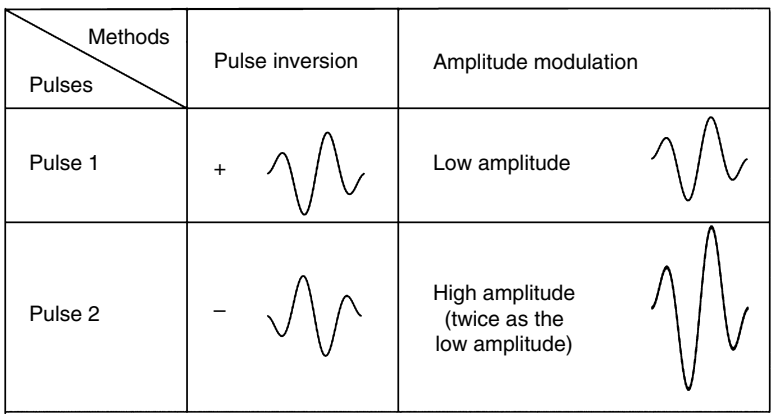

Figure 1.22 The pulse inversion and amplitude modulation methods for harmonic imaging.

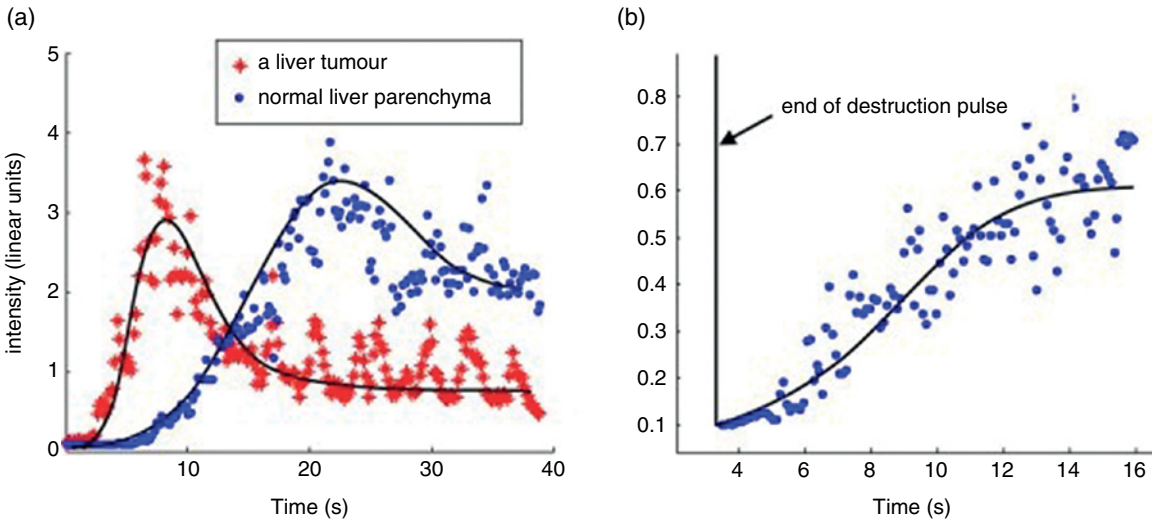

Figure 1.23 Clinical examples of a time–intensity curve for (a) a bolus injection in a liver; and (b) constant infusion with destruction–replenishment in the myocardium. Oscillations in the signals were mainly caused by tissue motion during imaging, while in (b) cardiac systole may also have contributed to the oscillation. Note that the *y*-axes between (a) and (b) are not comparable as they were acquired with different scanner settings on different patients. *Source:* Tang, M.-X., Mulvana, H., Gauthier, T. et al. (2011), *Interface Focus*, 1(4): 1520–1539. Reproduced with permission of The Royal Society.

uptake of the bubbles can thus be measured as a function of time. Quantification of CEUS can be based on image intensity or the timing of the tissue uptake of the bubbles. A curve of image intensity versus time (the so-called time–intensity curve, TIC) can be produced for any pixel or region of interest within the image plane. Such a curve contains information on tissue perfusion. Two types of TIC can be obtained, depending on whether the bubbles are administered as a bolus injection or via a constant infusion. A bolus is relatively simple to administer and more common in clinical practice, while a constant infusion is often combined with a 'destruction–replenishment' mode in which higher-MI ultrasound pulses are used to destroy the bubbles in the imaging plane, followed by low-MI ultrasound pulses to monitor replenishment in the tissue. This technique is unique to ultrasound, as no other clinical imaging modalities can deactivate their contrast-enhancing agents to create a new input function. Examples of the two types of TIC are shown in Figure 1.23.

Elastography

Tissue stiffness carries diagnostic information: for example, cancerous tissue is usually harder than normal tissue. Manual palpation, such as in the breast, has been proven to be effective, but only for shallow targets, and it is subjective. Elastography uses imaging to non-invasively detect internal tissue displacement as a result of applied forces, based on which a map of tissue elasticity property can be obtained. For example, in Figure 1.24, if we have an imaging tool to show

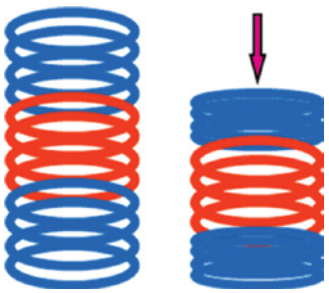

Figure 1.24 Principle of elastography: the blue spring, which simulates soft tissue, compresses more under force than the red spring, which simulates harder tissue. An elastography system can measure the compression of different tissue under force and hence detect their stiffness.

that the red part of the spring is harder to compress, then we will know that part is stiffer than the rest of the spring.

There are a few key quantities in tissue elastography. The first is tissue displacement, which can be measured using imaging and target tracking. The second is stress, which is the applied force per unit area and has units of pressure. The third is strain, ε, which is the fractional change in length, that is, the ratio of total deformation to the initial dimension of the material body, $\varepsilon = \Delta L/L$. Here L is the initial dimension and delta L is the deformation due to the applied force.

An elastography was initially defined as a strain image, but it is not quantitative, and the strain value does not only depend on tissue stiffness. Young's modulus (E), $E = \sigma/\varepsilon$, which describes longitudinal deformation in terms of strain ε in response to longitudinal stress σ, and the tissue shear modulus, which relates transverse strain to transverse stress,

are found to be useful tissue stiffness parameters. Such parameters can be obtained by matching the displacements measured from ultrasound images before and after force is applied with those calculated based on a theoretical tissue deformation model with tissue stiffness parameters.

Shear Wave Elastography

A more recent advance to quantitatively measure tissue stiffness is shear wave elastography. In a shear wave, tissue oscillates perpendicularly to the direction of wave propagation. This is in contrast to a longitudinal wave, where tissue oscillates in the same direction as wave propagation. Such a shear wave can be generated through an external mechanical force, or via a push within the tissue remotely generated by ultrasound. When ultrasound is scattered, reflected, or absorbed, energy and momentum are transferred to the medium, inducing a force, termed an acoustic radiation force (ARF). Such an ARF can be used to remotely push tissue at a certain location and generate shear waves originating from this location non-invasively.

Shear wave elastography is based on the relationship in Equation 1.7 between tissue shear modulus μ, tissue density ρ, and shear wave velocity c:

$$c_{SH} = \sqrt{\frac{\mu_{SH}}{\rho}} \tag{1.7}$$

Assuming a known and constant density of the tissue, the tissue shear modulus μ can be calculated if we know the shear wave velocity c. This velocity can be obtained by ultrasound imaging of the tissue displacement due to the shear waves. Tissue displacement can be obtained by comparing the beamformed image data between consecutive frames through cross-correlation, for instance. When the shear wave passes a certain spatial location in the image, its tissue displacement will increase and decrease over time, as shown in Figure 1.25. If we observe the tissue displacements over time at two chosen spatial positions with known distance, we can calculate the shear wave velocity by dividing the distance by the time difference between the two peaks in Figure 1.25.

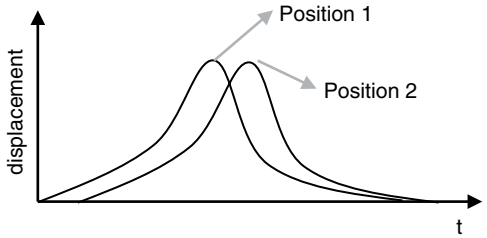

Figure 1.25 Principle of shear wave elasticity estimation: the two curves show tissue displacements at two spatial positions over time, measured by the imaging system. As the spatial distance and time of peak displacement between the two positions are known, shear wave velocity can be calculated, based on which the average shear modulus between the two spatial points can be estimated.

Given that typical shear wave velocity in soft tissue is in at least metres per second, and an ultrasound imaging field of view is typically a few centimetres, a very high image frame rate, typically at thousands of frames per second, is required to capture the shear wave propagation in the tissue in order to calculate the spatially resolved local velocity distributions.

Ultrasound Imaging Artefacts

Ultrasound images usually contain not only information on tissue structure and function, but also some features and interferences, including speckle, noise, and artefacts. These three features exist in almost all ultrasound imaging modes due to the underlying physics and assumptions made in the imaging. It is important for users to understand these features so that the images can be better interpreted in the diagnosis.

Noise

In a broad sense, there are two types of noise in ultrasound imaging, electronic noise and acoustic noise. The first type is the noise generated by the electronics and can be measured by the SNR. Averaging between consecutive frames of the images could increase the SNR, but it will also bring down the frame rate (temporal resolution). The SNR could also be increased by transmitting at a higher acoustical power, up to the safety limit. The second type of noise is called acoustic noise, which is commonly referred to as the speckle pattern, explained below.

Speckles

Speckles refer to the granular texture in images generated due to the scattering of waves by multiple and closely situated sub-wavelength scatters. As explained previously, an ultrasound system has certain spatial resolutions in a 3D space, which is typically of an order of more than a wavelength. This means that any objects/scatters much smaller than a wavelength cannot be resolved as separate objects. This volume is often called the sample volume. As a result, the brightness of the corresponding pixel in the image is formed by the coherent addition of echoes from all scatters within the sample volume. This coherent addition produces a granular texture called speckle in B-mode images (Figure 1.26). It is tempting to imagine that the speckle pattern represents the true structure within the sample volume. However, this is not the case, and the speckle patterns appear random and are often perceived as noisy, although this pattern is determined once the positions of the scatters and the transducer are determined. Therefore, the speckle patterns do contain information on the underling tissue