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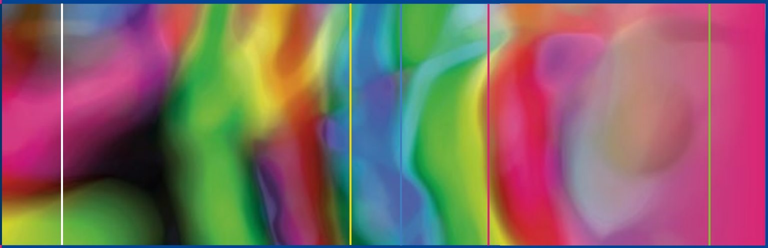

Thyroid and Parathyroid Ultrasound and Ultrasound-Guided FNA

Fourth Edition

Springer

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Foreword

Fourth Edition of the "Thyroid and Parathyroid Ultrasound and Ultrasound-Guided FNA"

When I began my career in endocrinology in 1971, and specifically in thyroidology, evaluation of the thyroid nodule simply involved a careful history and physical examination, as well as, in some cases, nuclear scanning. Ultrasound and, for that matter, other imaging techniques were not available. Despite what seems crude by today's standards, we thought we did pretty well. Then, years later, thyroid ultrasound became available, and that revolutionized our approach to patient evaluation and management and especially, with the additional advent of fine needle aspiration, to cytologic evaluation of nodules. Indeed, thyroid ultrasound has become standard practice in the evaluation of patients with thyroid nodules; it is an indispensable extension of our eyes and fingers.

In this fourth edition of the "Thyroid and Parathyroid Ultrasound and Ultrasound-Guided FNA" by Duick, Levine, and Lupo, the authors manage to synthesize the essentials of their prior three editions and provide a comprehensive and expanded review on the latest in the diagnosis and management of thyroid nodules, as well as focusing on parathyroid disease and non-endocrine lesions of the neck. They rely not only on their extensive collective clinical experience but on reviews of prior and current peer-reviewed publications. The authors, all experts in thyroid and parathyroid disease, cover not only thyroid and parathyroid disease but also have a chapter on imaging of the salivary glands and other non-endocrine lesions of the neck, mindful of the fact that those of us who perform (and evaluate) neck ultrasound also detect non-thyroid and parathyroid lesions. In this edition, the authors expand the chapters on both surgical and nonsurgical management.

Since the publication of the third edition of this book, the use of molecular markers in thyroid evaluation has become both more sensitive and specific, and an excellent chapter addresses this issue.

Finally, as more endocrinologists and surgeons perform ultrasounds in their office practices, it is essential that detailed reports are available to referring physicians and that they also include adequate information for billing purposes. The authors recognize this and include a chapter on authoring ultrasound reports.

In summary, this fourth edition brings together the collective wisdom of specialists who treat patients with thyroid nodules, thyroid cancer, and parathyroid disease and should serve as the "go-to" source for surgeons, endocrinologists, fellows, and residents.

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Preface

Fourth Edition of the Thyroid Ultrasound and Ultrasound-Guided FNA Textbook

Ultrasound has become ingrained as the classical utilization of applied technology for both diagnostic and interventional therapeutic approaches to the management of thyroid and parathyroid conditions. It is an invaluable tool for the practice of thyroidology and is most beneficial when performed in real time by a physician or a practitioner who is skilled and knowledgeable in the anatomy of the neck.

The recognition of imagery patterns suggestive of a generalized disease state, the presence and evaluation of thyroid nodules, the search for a parathyroid tumor when there is biochemical evidence of hyperparathyroidism, and the assessment for residual tissue and lymphadenopathy of the postoperative thyroid cancer neck are all related issues that ultrasound is capable of optimally imaging.

There continues to be technologic advances in demonstrating ultrasound images on the visual screen which enhance gray scale and employ both color flow Doppler and power Doppler which add additional information to the analysis of the thyroid gland, parathyroid tumors, and lymph nodes as well as other structures in the neck.

Ultrasound remains the number one invaluable tool for assessing the endocrine neck, and the performance of real-time ultrasound is unquestionably the optimum methodology for utilization.

Scottsdale, AZ, USA Daniel S. Duick, MD, MACE

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Chapter 1
History of Thyroid Ultrasound

Robert A. Levine and J. Woody Sistrunk

Abbreviations

AACE	American Association of Clinical Endocrinologists
AIUM	American Institute of Ultrasound Medicine
ATA	American Thyroid Association
ECNU	Endocrine Certification in Neck Ultrasound
MHz	Megahertz

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Introduction

The visual application of sound in medicine has revolutionized the diagnosis and management of thyroid disease. The safety of ultrasound, along with improvements in image quality and equipment availability, underlies the importance of thyroid ultrasound to today's endocrinologist and endocrine surgeon.

The thyroid is amenable to ultrasound study because of its superficial location, vascularity, size, and echogenicity [1]. In addition, the thyroid has a very high incidence of nodular disease, the vast majority benign. Most structural abnormalities of the thyroid need evaluation and monitoring but may not require intervention [2]. Between 1965 and 1970, there were seven articles published specific to thyroid ultrasound. In the last 5 years, there have been over 10,000 articles published. Thyroid ultrasound has undergone a dramatic transformation from the cryptic deflections on an oscilloscope produced in A-mode scanning, to barely recognizable B-mode images, followed by initial low-resolution gray scale, to current high-resolution images. Recent advances in technology, including harmonic imaging, spatial compound imaging, elastography, and three-dimensional reconstruction, have all furthered the field.

The development of high-resolution thyroid ultrasound required decades of study in both the acoustics of sound and data processing. Some animals, for example, dolphins and bats, have the ability use ultrasound in their daily activities in everything from catching prey to finding a mate. As early as the 1700s, the Italian biologist Lazzaro Spallanzani demonstrated that bats use high frequency sound waves to navigate in complete darkness [3]. The aim of this chapter is provide an overview of the basic advancements in the field of ultrasound that have provided the ability to easily and safely see and interpret structures inside the neck.

Beginnings of Ultrasound History

One of the earliest experiments regarding transmission of sound was performed in 1826 in Lake Geneva by Jean-Daniel Colladon. Using an underwater bell he determined the speed of sound transmission in water. In the 1800s, properties of sound including wave transmission, propagation, reflection, and refraction were defined. In 1877 Lord Rayleigh's English treatise, "Theory of Sound," added mathematics and became the basis for the applied study of sound. The principles described lead to the science of using reflected sound in identifying and locating objects. In 1880, Pierre and Jacques Curie discovered the piezoelectric effect, determining that an electric current applied across a crystal would result in a vibration that would generate sound waves and that sound waves striking a crystal would, in turn, produce an electric voltage. Piezoelectric transducers were capable of producing sonic waves in the audible range and ultrasonic waves above the range of human hearing [3].

Sonar

The first patent for a sonar device was issued to Lewis Richardson, an English meteorologist, only 1 month after the Titanic sank following collision with an iceberg. The first functional sonar system was made in the United States, by Canadian Reginald Fessenden, in 1915. The Fessenden "fathometer" could detect an iceberg 2 miles away. As electronics improved, Paul Langevin designed a device called a hydrophone. It became of the one of the first measures available to detect German U-Boats during World War I. The hydrophone was the basis of the pulse-echo sonar that is still employed in ultrasound equipment today [3, 4].

Rudimentary high frequency ultrasound analysis was used on a commercial basis in the 1930s and 1940s to detect defects in steel such as the hull of a ship. Although crude by today's standards, inhomogeneity suggested abnormalities, whereas a flawless appearance suggested uniform material [4]. With the end of World War II, the development of the computer and the invention of the transistor advanced the development of medical ultrasound [3].

Early Medical Applications of Ultrasound

The initial use of ultrasound in medicine in the 1940s was therapeutic rather than diagnostic. Following the observation that very high-intensity sound waves had the ability to damage tissues, lower intensities were tried for therapeutic uses. Focused sound waves were used to mildly heat tissue for therapy of rheumatoid arthritis, and early attempts were made to destroy the basal ganglia to treat Parkinson's disease [4]. The American Institute of Ultrasound in Medicine (AIUM) was formed in 1952 with therapeutic ultrasound in physical medicine being the primary focus. Although members performing diagnostic ultrasound were not accepted until 1964, diagnostic ultrasound is currently the primary focus of this organization [3].

Early in the twentieth century, Paul Langevin described the ability of high-intensity ultrasound to induce pain in a hand placed in a water tank. The 1940s saw therapeutic ultrasound tried in numerous applications ranging from gastric ulcers to arthritis. Attempts to destroy the basal ganglia in patients with Parkinson's disease now seem archaic. At the time therapeutic ultrasound was headed toward the museum of medical quackery, consideration of ultrasound as a diagnostic tool in medicine had begun. Although Drs. Gohr and Wedekindt at the Medical University of Koln, Germany, suggested that ultrasound could detect tumors, exudates, and abscesses, the results were not convincing. Karl Theodore Dussik is credited as the first physician to use diagnostic ultrasound. In his 1952 report, "Hyperphonography of the Brain," ultrasound was utilized in localizing brain tumors and the cerebral ventricles by transmitting ultrasonic sound through the skull. While the results of these studies were later discredited as predominantly artifact, this work played a significant role in stimulating research into the diagnostic capabilities of ultrasound [3].

A-Mode Ultrasound

One of the first studies of diagnostic ultrasound was performed by George Ludwig. Using A-mode ultrasound, his main focus was using ultrasound to detect gallstones, shown as reflected sound waves on an oscilloscope screen. Through his study of various tissues, including the use of live subjects, clinical utility of diagnostic ultrasound was described. Despite the limited efficacy of his rudimentary ultrasound system, Ludwig's most important achievement may be his determination of the velocity of sound transmission in animal soft tissues. Ludwig also determined that the optimum frequency of an ultrasound transducer for deep tissue was between 1 and 2.5 MHz. The ultrasound characteristics of mammalian tissue were further defined by physicist Richard Bolt at Massachusetts Institute of Technology and neurosurgeon H. Thomas Ballantine, Jr. at Massachusetts General Hospital [3].

Most of early ultrasound used a transmission technique, but by the mid-1950s that was supplanted by a reflection technique. Providing information limited to a single dimension, A-mode scanning showed deflections on an oscilloscope indicating distance to reflective surfaces [4] (see Fig. 2.7). A-mode ultrasonography was used for detection of brain tumors, shifts in the midline structures of the brain, localization of foreign bodies in the eye, and detection of detached retinas [4]. In the first presage that ultrasound may assist in the detection of cancer, John Julian Wild reported the observation that gastric malignancies were more echogenic than normal gastric tissue. Along with Dr. John Reid, he later studied 117 breast nodules using a 15 MHz sound source and reported the ability to determine their size with an accuracy of 90% [3].

B-Mode Ultrasound

During the late 1950s, the first two-dimensional B-mode scanners were developed. B-mode scanners display a compilation of sequential A-mode images to create a two-dimensional image (see Fig. 2.8). Douglass Howry developed an immersion tank B-mode ultrasound system which was featured in the Medicine section of Life Magazine in September 1954 [3]. Several additional models of immersion tank scanners followed. All utilized a mechanically driven transducer that would sweep through an arc, with an image reconstructed to demonstrate the full sweep. Continued development led to the "Pan-scanner," a more advanced B-mode device, but it still employed a cumbersome bathtub of water. Later advances included a handheld transducer that still required a mechanical connection to the unit to provide data regarding location and water-bag coupling devices to eliminate the need for immersion [3].

By 1964, the work of Joseph H. Holmes along with William Wright and Ralph (Edward) Meyerdirk lead to the prototype of the "compound contact" scanner, with direct contact of the transducer with the patient's body. As stated in a 1958 Lancet article describing ultrasound evaluation of abdominal masses, "Any new technique becomes more attractive if its clinical usefulness can be demonstrated without harm, indignity or discomfort to the patient" [5].

Applying Ultrasound Technology to the Thyroid

The 1960s brought continued development of microelectronics including semiconductors that revolutionized the ability to process signals and produce visual displays. The phased array transducer utilized in modern day ultrasound derived from highly classified submarine technology. During the 1970s additional advances in transducer design, including the linear array and mechanical oscillating transducers, lead to the two-dimensional imaging which remains the standard today. With these improvements and the addition of gray-scale displays, ultrasound representation of the thyroid began to resemble that seen in the operative field or gross anatomy lab [4].

In 1967 Fujimoto reported data on 184 patients studied with a B-mode ultrasound "tomogram" utilizing a water bath [6]. The authors reported that no internal echoes were generated by the thyroid in patients with normal thyroid function and non-palpable thyroid glands. They described several basic patterns generated by palpably abnormal thyroid tissue. Thyroid tissue with strong internal echo attenuation characteristics was considered "malignant." Unfortunately, 25% of benign adenomas showed the malignant pattern, and 25% of papillary carcinomas were found to have the benign pattern. Although the first major publication of thyroid ultrasound attempted to establish the ability to determine malignant potential, the results were nonspecific in a large percentage of the cases. However, this was a seminal paper in ultrasound and is considered the first on thyroid ultrasound to attempt to establish the malignant appearance of nodules [4, 6].

In 1971 Manfred Blum published a series of A-mode ultrasounds of thyroid nodules (see Fig. 2.7). He demonstrated the ability of ultrasound to distinguish solid from cystic nodules, as well as accuracy in measurement of the dimensions of thyroid nodules [7]. Additional publications in the early 1970s further confirmed the capacity for both A-mode and B-mode ultrasound to differentiate solid from cystic lesions but consistently demonstrated that ultrasound was unable to distinguish malignant from benign solid lesions with acceptable accuracy [8].

The advent of gray-scale display resulted in images that were far easier to view and interpret [6]. In 1974 Ernest Crocker published *The Gray Scale Echographic Appearance* *of Thyroid Malignancy*. Using an 8 MHz transducer with a 0.5 mm resolution, he described "low amplitude, sparse and disordered echoes" characteristic of thyroid cancer when viewed with a gray-scale display [9]. The pattern felt to be characteristic of malignancy was what would now be considered "hypoechoic and heterogeneous".

With each advance in technology, interest was rekindled in ultrasound's ability to distinguish benign from malignant lesions. Initial reports of ultrasonic features typically described findings as being diagnostically specific. Later, reports followed showing overlap between various disease processes. For example, following an initial report that the "halo sign," a rim of hypoechoic signal surrounding a solid thyroid nodule, was seen only in benign lesions [10], Propper reported that two of ten patients with this finding had carcinoma [11]. As discussed in Chap. 7, the halo sign is still considered to be one of the numerous features that can be used in determining the likelihood of malignancy in a nodule.

In 1977 Walfish recommended combining fine-needle aspiration biopsy with ultrasound in order to improve the accuracy of specimen acquisition [12]. Subsequent studies demonstrated that biopsy accuracy is greatly improved when ultrasound is used to guide needle placement. Most patients with prior "nondiagnostic" biopsies will have an adequate specimen obtained when ultrasound-guided biopsy is performed [13]. Ultrasound-guided fine-needle aspiration results in improved sensitivity and specificity, as well as a greater than 50% reduction in nondiagnostic and false-negative biopsies [14].

Over the past several years, the value of ultrasound in screening for suspicious lymph nodes prior to surgery in patients with biopsy proven cancer has been established. Current guidelines for the management of thyroid cancer indicate a pivotal role for ultrasound in monitoring for locoregional recurrence [15].

During the 1980s Doppler ultrasound was introduced, allowing detection of blood flow in tissues. As discussed in detail in Chap. 3, the role of Doppler in assessing the likelihood of malignancy has undergone a recent reevaluation. Doppler imaging may demonstrate the increased blood flow characteristic of Graves' disease [16] and may be useful in distinguishing between Graves' disease and thyroiditis, especially in pregnant patients or when radioisotope scanning is unavailable (see Chap. 3). Doppler imaging is useful in determining the subtype of amiodarone-induced thyrotoxicosis [17].

Recent Advances in Technology

Recent technological advancements include intravenous sonographic contrast agents, three-dimensional ultrasound imaging, and elastography. Intravenous sonographic contrast agents are available in Europe but remain experimental in the United States. All ultrasound contrast agents consist of microspheres, which function both by reflecting ultrasonic waves and, at higher signal power, by reverberating and generating harmonics of the incident wave. Ultrasound contrast agents have been predominantly used to visualize large blood vessels and have shown promise in imaging peripheral vasculature as well as liver tumors and metastases [18]. While no studies have been published demonstrating any advantage of contrast agents in routine thyroid imaging, the use of contrast agents or B-flow imaging may be helpful in the immediate assessment of successful laser or radiofrequency ablation of thyroid nodules [19].

Three-dimensional display of reconstructed images has been available for CT scan and MRI for many years and has demonstrated practical application. While three-dimensional ultrasound has gained popularity for fetal imaging, its role in diagnostic neck ultrasound remains unclear. Obstetrical ultrasound has the great advantage of the target being surrounded by a natural fluid interface, greatly improving surface rendering, whereas 3D thyroid ultrasound is limited by the lack of a similar interface distinguishing the thyroid from adjacent neck tissues. It has been predicted that breast biopsies may eventually be guided in a more precise fashion by real time 3D imaging [20], and it is possible that, in time, thyroid biopsy will similarly benefit. At present, however, 3D ultrasound technology does not provide a demonstrable advantage in thyroid imaging.

Elastography is a promising technique in which the compressibility of a nodule is assessed by ultrasound, while external pressure is applied. With studies showing good predictive value for detection of malignancy in breast nodules, recent investigations of its role in thyroid imaging have been promising. Additional prospective trials are ongoing to assess the role of elastography in predicting the likelihood of thyroid malignancy. The role of elastography in the selection of nodules for biopsy or surgery is discussed in Chap. 16.

Application of Neck Ultrasound by Endocrinologists and Endocrine Surgeons

With the growing recognition that real time ultrasound performed by a clinician provides far more useful information than that obtained from a radiology report, point of care ultrasound has gained acceptance. The first educational course specific to thyroid ultrasound was offered in 1998 by the American Association of Clinical Endocrinologists (AACE). Under the direction of Dr. H. Jack Baskin, 53 endocrinologists were taught to perform diagnostic ultrasound and ultrasound-guided fine-needle aspiration biopsy. By the turn of the century, 300 endocrinologists had been trained. Endocrine University, established in 2002 by AACE, began providing instruction in thyroid ultrasound and biopsy to all graduating endocrine fellows. By 2016 over 6000 endocrinologists had completed an AACE ultrasound course. In 2007 a collaborative effort between the American Institute of Ultrasound in Medicine (AIUM) and AACE established a certification program for endocrinologists trained in neck ultrasound. By 2016 the ECNU (Endocrine Certification in Neck Ultrasound) program had certified over 470 endocrinologists as having the training, experience, and expertise needed to perform thyroid and parathyroid ultrasound and fine-needle aspiration biopsy. In 2011 the American Institute of Ultrasound in Medicine began accrediting qualified endocrine practices as centers of excellence in thyroid and parathyroid imaging. To date, 89 practices have received AIUM site accreditation in thyroid and parathyroid ultrasound.

Conclusion

When the American Association of Clinical Endocrinologists began its efforts to teach thyroid ultrasound to Endocrinologists in 1998, an ultrasound machine seemed a foreign concept in the office. At present, it is becoming the exception to find endocrinologists who do not have thyroid ultrasound and ultrasound-guided FNA biopsy as part of their practice.

In parallel with the growth of thyroid ultrasound in endocrinology, the American Thyroid Association (ATA) guidelines for the management of thyroid nodules and thyroid cancer have placed an increasing emphasis on the sonographic characteristics of thyroid nodules. The 2006 guidelines mention ultrasound characteristics of thyroid nodules five times [21]. The 2009 ATA guidelines make 14 references to ultrasound characteristics [22], and the latest 2015 ATA guidelines mention ultrasound characteristics of thyroid nodules and thyroid cancer 100 times [15].

In the 50 years since ultrasound was first used for thyroid imaging, there has been a profound improvement in the technology and quality of images. The transition from A-mode to B-mode to gray-scale images was accompanied by dramatic improvements in clarity and interpretability of images. Current high-resolution images are able to identify virtually all lesions of clinical significance. Ultrasound characteristics can predict which nodules are likely to be benign and detect features including irregular margins, microcalcifications, and central vascularity that may deem a nodule suspicious [4]. Ultrasound plays a clear fundamental role in thyroid nodule and lymph node evaluation as well as the selection of which should undergo biopsy [15]. Ultrasound has proven utility in the detection of recurrent thyroid cancer in patients with negative whole body iodine scan or undetectable thyroglobulin [15, 23]. Recent advances including the use of contrast agents, tissue harmonic imaging, elastography, and multiplanar reconstruction of images have further enhanced the diagnostic value of ultrasound images. Ultrasound guidance of fine-needle aspiration biopsy has been demonstrated to improve both diagnostic yield and accuracy and has become the standard of care. Routine point of care use of ultrasound is often considered an extension of the physical examination by endocrinologists and endocrine surgeons. High-quality ultrasound systems are now available at prices that make this technology accessible to virtually all providers of endocrine care [4].

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Chapter 2

Thyroid Ultrasound Physics

Robert A. Levine

Abbreviations

Hz	Hertz
MHz	Megahertz
m/s	Meters per second

Sound and Sound Waves

Some animal species such as dolphins, whales, and bats are capable of creating a "visual" image based on receiving reflected sound waves. Our unassisted vision is limited to electromagnetic waves in the spectrum of visible light. Humans require technology and an understanding of physics to use sound to create a picture. This chapter will explore how we have developed a technique for creating a visual image from sound waves [1].

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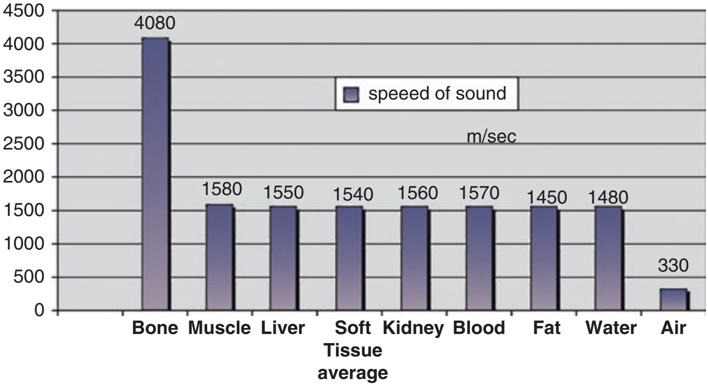

FIGURE. 2.1 Speed of sound. The speed of sound is constant for a specific material and does not vary with frequency. Speed of sound for various biological tissues is illustrated

Sound is transmitted as mechanical energy, in contrast to light, which is transmitted as electromagnetic energy. Unlike electromagnetic waves, sound waves require a propagating medium. Light is capable of traveling through a vacuum, but sound will not transmit through a vacuum. The qualities of the transmitting medium have a direct effect on how sound is propagated. Materials have different speeds of sound transmission and acoustic impedance. Speed of sound is constant for a specific material and does not vary with sound frequency (Fig. 2.1). Acoustic impedance is a measure of the opposition that a system presents to the flow of acoustic energy. When sound travels through a material and encounters a boundary separating two different areas of acoustic impedance, a portion of the sound energy will be reflected, and the remainder will be transmitted. The amount reflected is proportionate to the degree of mismatch of acoustic impedance. Acoustic impedance of a material depends on its density, stiffness, and speed of sound [2].

Sound waves propagate by compression and rarefaction of molecules in space (Fig. 2.2). Molecules of the propagating

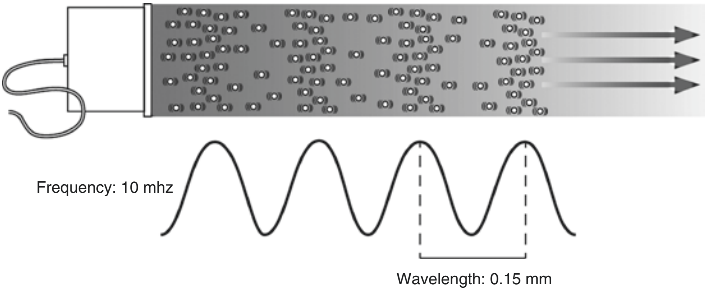

FIGURE. 2.2 Sound waves propagate in a longitudinal direction but are typically represented by a sine wave where the peak corresponds to the maximum compression of molecules in space, and the trough corresponds to the maximum rarefaction

medium vibrate around their resting position and transfer their energy to neighboring molecules. Sound waves carry energy rather than matter through space.

As shown in Fig. 2.2, sound waves propagate in a longitudinal direction but are typically represented graphically by a sine wave where the peak corresponds to the maximum compression of molecules in space, and the trough corresponds to the maximum rarefaction. Frequency is defined as the number of cycles per time of the vibration of the sound waves. A Hertz (Hz) is defined as one cycle per second. The audible spectrum is between 30 and 20,000 Hz. Ultrasound is defined as sound waves at a higher frequency than the audible spectrum. Typical frequencies used in diagnostic ultrasound vary between five million and sixteen million cycles per second (5 and 16 MHz) [1, 3].

Diagnostic ultrasound uses pulsed waves, allowing for an interval of sound transmission, followed by an interval during which reflected sounds are received and analyzed. Typically three cycles of sound are transmitted as a pulse. The spatial pulse length is the length in space filled by three cycles (Fig. 2.3). Spatial pulse length is one of the determinants of resolution. Since higher frequencies have a smaller pulse