FORUM

Medical ultrasound: Time-honored method or emerging research frontier?

Medical ultrasound is the most commonly used medical imaging modality worldwide. In the United States, for example, it was used in adults aged 18 - 64 years at a rate of 278 per 1000 patients in 2016, compared with 134 for X-ray tomography (CT), 85 for magnetic resonance imaging (MRI), and 16 for nuclear imaging (NM) [1]. Ultrasound diagnostic applications range from the head [2] to the toe [3] and from conception [4] to death [5]. In recent decades, new inventions have been made, old concepts have been revised and revived, and brought into clinical use in ultrasound imaging and therapy. This special issue, Recent Advances in Ultrasound Imaging, is intended to introduce some of these exciting developments to a wider readership.

Imaging applications of ultrasound technology show a wealth of ingenuity to overcome earlier obstacles. The first ultrasound images were produced with single-element piezoelectric transducers [6], which produced so-called A-mode (amplitude) lines displayed on oscilloscopes [7]. Antenna theory and imaging knowledge borrowed from radar led to the development of array-based [8] B-mode (brightness) images [9]. These show reflected or scattered acoustic waves as gray-scale encoded pixel intensities with spatial resolution. Initially, one-dimensional array technology could provide 2D images, i.e., depth resolution by time measurement assuming constant speed of sound and lateral resolution along the extent of the array. Later, two-dimensional arrays began to provide four-dimensional visualizations, i.e., time-resolved volumetric data sets. While these were initially realized by mechanically sweeping one-dimensional arrays, full three-dimensional beamforming is now possible by using two-dimensional apertures.

Traditionally, these have been implemented as arrays of diced piezoelectric crystals [10], which presents technical and cost challenges. With the turn of the millennium, a new technology emerged on the horizon of ultrasound generation: capacitive micromechanical ultrasonic transducers, abbreviated as cMUTs or CMUTs [11,12]. Greatly simplified, these devices can be thought of as miniature drumheads that bend due to capacitive charging effects. Photolithography can be used to realize electronic transmit and receive circuits and a large number of transmit/receive drums at very low cost. This makes CMUTs attractive and has led to many attempts to revolutionize the field of ultrasound diagnostics. Herickhoff and van Schaijk provide an overview of this technology and its challenges and opportunities.

Acoustic attenuation initially limited the use of high frequencies at greater depth due to the low signal-to-noise ratio. A coded excitation with matched filters was proposed to increase the dynamic range by 20 dB [13], resulting in a signal-to-noise ratio above 70 dB. Although system performance could be improved by increasing the transmit power, this is limited by the maximum sound power and sound pressure for patient safety. While acoustic waves propagate at different rates in different tissues of the human body, general ultrasound equipment assumes not only a constant speed of sound, but often a general speed of sound of 1,540 m/s. Devices are now capable of adapting to an application-specific adaptive sound velocity, which improves phase coherence and thus image quality. Breast tissue has an average sound velocity of 1,450 m/s versus the general sound velocity of 1,540 m/s. Reader studies have demonstrated image enhancements from altering the speed of sound [14], and algorithms have been developed to automatically find the optimal speed of sound [15].

Furthermore, the propagation of the acoustic wave is affected by nonlinear effects as well as spectral aberration and attenuation. To overcome this, methods such as software beamformers, coded excitation [13], and harmonic tissue imaging have been introduced. These methods have dramatically increased the need for faster processing. As graphics processing units (GPUs) and multicore central processing units (CPUs) enabled large computational power, developers were able to rethink ultrasound computed tomography. Analogous to X-ray-based CT, ultrasound computed tomography enables the unfolding of complex wave paths through tissue [16].

In this issue, Wiskin *et al*. demonstrate the complex imaging methods that are now possible, both in the analytical framework of wave propagation and from numerical and computational perspectives. Ultrasound-based volumetric breast imaging has now reached a level of detail otherwise known only from magnetic resonance imaging.

While the technology presented by Wiskin *et al*. requires specialized hardware, Ali *et al*. present a review of approaches to aberration correction based on pulse-echo imaging, i.e., non-tomographic imaging. Overcoming or at least reducing aberration allows for much better spatial resolution and image contrast, which will benefit clinicians. An excellent byproduct of this process is the simultaneous assessment of local sound velocity, which in itself can be a diagnostic tool.

Physical effects associated with acoustic wave propagation have been discovered and exploited to further improve image quality and thus the diagnostic value of ultrasonogra-

Z Med Phys **xxx** (2023) xxx–xxx
https://doi.org/10.1016/j.zemedi.2023.05.005
www.elsevier.com/locate/zemedi

phy. A significant increase in signal-to-noise ratio was observed in ultrasonography and was associated with minibubbles produced by intracardiac injection of saline [17]. A contrast agent for ultrasonography was born and subsequently developed and engineered [18].

Note that the frequency-dependent peak signal for contrast agents with a radius of 3 μm is about 1 MHz. This is remarkable for two reasons. First, it is fortunate that bubbles small enough to penetrate the vascular capillary bed resonate at ultrasound frequencies low enough to penetrate the human body. Second, it is surprising that 1 MHz excitation in soft tissue at 1,540 m/s yields a wavelength of 1.5 mm, which is very large compared to a 6-μm bubble. Therefore, these contrast agents follow Rayleigh scattering, i.e., $k \cdot a \ll 1$, here $k \cdot a \quad 0.02$, where k is the wavenumber and a is the diameter of the bubbles. The logical conclusion is that ultrasonography should not be able to spatially localize individual bubbles. However, statistical analysis based on light microscopic methods [19] allows visualization of the vascular capillary bed [20].

In this issue, Dencks *et al*. provide an overview of the field of ultrasound localization microscopy. They report how the resolution limit of conventional ultrasound can be overcome, allowing microscopic localization of micrometer-sized contrast bubbles in vivo. A resolution of 9 to 34 μm can be achieved with an imaging system of 15 MHz and a natural wavelength of 102 μm. Bubble concentration is a parameter that can be adjusted to be sufficient for efficient sampling of thousands or millions of capillaries while preventing spatial ambiguities due to overlapping point distribution functions by falling below a lower mean distance between bubbles, i.e., maintaining a surrogate population. As tissue motion can lead to loss of spatial reference, compensation and tracking methods are reviewed.

Song *et al*. discuss whether super-resolution ultrasound is ready for clinical use. The ability to resolve microvessels and preserve vascular morphology is a concept that has significantly changed the way ultrasonography is viewed. For angiographic purposes, it is now possible to penetrate acoustically into the lower micrometer range. Optical methods offer high detail, i.e., high resolution, but cannot penetrate deeper than a few tens of millimeters into soft tissue. At the same time, ultrasound has been limited by its native wavelengths, which undergo frequency-dependent attenuation, so that the achievable wavelength at depths exceeding the optical penetration depth is more than 100 μm. However, since bubbles scatter in the Rayleigh range, a spatial resolution of less than 10 μm can be achieved at depths greater than 10 cm, which can be considered remarkable.

In addition to the usual physical effects of sound waves and their propagation, there are other physical effects that can produce sound waves. The most profound is the experience of lightning and thunder, that is, the generation of sound by the sudden thermal expansion of the atmosphere, which in turn is due to the massive electric current of the lightning strike. Within ten microseconds, the atmosphere heats up to several tens of thousands of Kelvin, generating sound pressure levels of up to 200 dB [21]. The same concept can be applied to medical ultrasound [22,23]. Photoacoustics utilizes the energy absorption of hemoglobin when exposed to light. Illuminating blood with laser light can produce ultrasound signals in the megahertz range. Specific selection of optical frequencies can distinguish between oxygenated and deoxygenated hemoglobin [24]. When using a clinical ultrasound scanner in receive-only mode, these acoustic emissions can be directly visualized. In this way, it is not the acoustic backscattering of tissues that can be imaged, but rather their ability to produce sound in response to a specific stimulus. In addition, thermal imaging has also been identified as a potential tool for diagnostic or therapeutic guidance [25]. Some of the current photoacoustic research is focused on clinical applications.

Pattyn *et al*. highlight strategies for spectroscopic assessments in a tomographic setup where wave propagation can be more fully acquired and understood to overcome artifacts that result from heterogeneities, similar to the efforts described above on ultrasound CT.

The wealth of clinical applications that could benefit from photoacoustics is illustrated in the contribution by Ni *et al*. They showcase examples in musculoskeletal imaging, inflammatory bowel disease, and cancer (colorectal, ovarian, prostate, and cervical). Smart integration of photoacoustics with traditional pulse-echo ultrasound (B-mode and flow-modes) will be able to deliver a more detailed picture of the underlying anatomy and physiology.

More and more parts of the body are being examined with ultrasound. One very innovative application is the focus of the review by Rodriguez *et al*., namely the oral cavity, more specifically periodontal tissue. The miniaturization of ultrasound transducers and the use of higher frequencies, previously associated only with dermatologic and intraoperative applications, have enabled the use of ultrasound as a new modality. For periodontists and possibly dentists in general, this is a welcome tool that provides excellent soft tissue contrast and does not require ionizing radiation.

Ultrasound is a safe and effective imaging modality, and undesirable bioeffects are virtually unknown [26]. In contrast, however, ultrasound can produce biological effects when intended. Lithotripsy is a well-established method for disintegration of kidney stones [27], and newer therapies include essential tremor [28], uterine fibroids [29], prostate [30], and breast cancer [31].

Two main categories of ultrasound therapies are often distinguished, those that use heating of the tissue caused by viscous effects, i.e., hyperthermia, and those that rely on the instantaneous impulse of the sound wave leading to

Please cite this article in press as: Kripfgans O. D. and Sekine Y. Medical ultrasound: Time-honored method or emerging research frontier?. Z Med Phys (2023), https://doi.org/10.1016/j.zemedi.2023.05.005

mechanical effects, i.e., cavitation. Lithotripsy may have been the first established therapeutic application that utilized cavitation-based bioeffects. Recently, researchers have rediscovered this principle to fracture soft tissue, i.e., histotripsy [32]. However, therapeutic applications also include sophisticated approaches that go beyond direct tissue destruction. Acoustic droplet vaporization has been introduced [33] as a method for super-catheterization, tissue occlusion [34], or drug delivery [35]. Neurostimulation [36] and blood-brain barrier opening [37] are other examples of the power of intended and thus controlled bioeffects. In this special issue, two therapeutic applications of ultrasound are presented.

Aliabouzar *et al*. review concepts of acoustic droplet evaporation with emphasis on nucleation and dynamics of evaporation. This involves exposing perfluorocarbon droplets in the micrometer diameter range to high-intensity ultrasound, which triggers a phase change from liquid to gaseous perfluorocarbon. Often, these droplets are already in a superheated state, but this need not be the case, as they can also transition to a supercooled state.

Sharma *et al*. provide an overview of the improvement of cavitation-based therapies. While it is known that acoustically driven inertial cavitation of gas bubbles can damage and kill cells in the human body, it has also been found that adjacent endothelial cells experience radiation sensitization as a byproduct. In other words: After focused ultrasound treatment of a particular breast lesion and with contrast bubbles in the region of interest, the soft tissue is weakened in terms of its response to radiation therapy. While ultrasound and radiation both have therapeutic effects individually, the combined effect is greater than their sum and has been shown to bypass the long-sought method of reliably apoptosing endothelial cells without damaging surrounding normal tissue.

Many factors have contributed to the phenomenal advances that ultrasonography has made over the past 50 years. Some of these are discussed in detail in this special issue. The physical window of available data still offers years of ingenuity to improve imaging, interpretation, and new applications. Even when the underlying physics seems to stand in the way of a particular path for further progress, researchers seem to be finding alternatives, such as with ultrasound localization microscopy. Artificial intelligence and even more computing power are likely to give us medical imaging capabilities that we dream about today but will take for granted tomorrow.

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Please cite this article in press as: Kripfgans O. D. Medical ultrasound: Time-honored method or emerging research frontier?. Z Med Phys (2023), https://doi.org/10.1016/j.zemedi.2023.05.005