Applications of Ultrasound in Medical Science: A Review

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Abstract: ***The applications during last two decades and current investigations on the application during half decade of ultrasound in the field of medical sciences are presented in this paper. Present study has been focused on the latest advances in the applied ultrasound technology in the medical instrumentations. SAIJO, Yoshifumi has reported the development of ultrasound microscope systems which realized the resolution of 15-micron with 100 MHz and resolution to visualize a single cell with GHz range ultrasound. Ultrasonic imaging provides not only tissue morphology but also tissue elasticity. The CNRS has reported a new ultrasound imaging technique, the first ever in visualization of activity in the periform cortex of rats during odor perception. This work of CNRS also sheds new light on the still poorly known functioning of the olfactory system, and notably how information is processed in the brain. The Clot Bust ER®, a device patented by scientist Culp from University of Arkansas at Little Rock, delivers therapy to quickly bust clots that cause stroke and it improves the clot-busting drug by 40 to 50 percent. The ultrasound stirs the drug around, making it work better. The size of molecules penetrating the blood-brain barrier (drug delivery) can be controlled using the pressure of an ultrasound beam to let specific molecules through, a new technique demonstrated for the first time by Columbia University School of Engineering and Applied Science. The ultrasound and magnetic resonance imaging (MRI) are used to destroy a tumor in leg without piercing the skin. Doctors used an MRI to guide high-intensity ultrasound waves to destroy a benign bone tumor called osteoid osteoma. Melanoma is the deadliest form of skin cancer, causing more than 75 percent of skin-cancer deaths. Now, a team of researchers has developed a new hand-held device that uses lasers and sound waves to treat and diagnose melanoma. A transcranial ultrasound therapy can potentially be applied to the treatment of brain tumors and targeted drug delivery. Doctors in California are the first to use a new ultrasound technique to assess fallopian tubes by employing a mixture of saline and air bubbles that is less painful, avoids X-ray exposure and is more convenient to patients. Researchers from Biophysical Society have developed a new non-contact, non-invasive tool to measure the mechanical properties of cells at the sub-cell scale with high-frequency sound. North Carolina State University demonstrate a new ultrasound device that could help to identify arterial plaque that is at high risk of breaking off and causing heart attack or stroke has been developed by researchers. The results of detailed reviews on fascinating areas of medical ultrasound techniques and their applications will be discussed and presented in the talk.***

Keywords: Ultrasound, heart attack, Brain Tumor, Melanoma, Osteoid Osteoma, Single cell, Nanorotor, Olfactory system, Drug Delivery

1. Introduction

In physics the term “ultrasound” applies to all acoustic energy with a frequency above human hearing (20,000 hertz or 20 kilohertz). Typical diagnostic sonographic scanners operate in the frequency range of 2 to 18 megahertz, hundreds of times greater than the limit of human hearing. Higher frequencies have a correspondingly smaller wavelength, and can be used to make sonograms with smaller details. [1]Diagnostic sonography (ultrasonography) is an ultrasound-based diagnostic imaging technique used to visualize subcutaneous body structures including tendons, muscles, joints, vessels and internal organs for possible pathology or lesions. Sonography is effective for imaging soft tissues of the body. Sonographers typically use a hand-held probe (called a transducer) that is placed directly on and moved over the patient. A water-based gel is used to couple the ultrasound between the transducer and patient [1].

The application of ultrasound in medicine began in fifties of last century. First was introduced in the obstetrics, and after that in all the fields of the medicine (the general abdominal diagnostics, the diagnostics in the field of the pelvis, cardiology, ophthalmology and orthopedics and so on) (3). From the clinical aspect the ultrasound possesses the priceless significance because of its noninvasive, good visualization characteristics and relatively easy management [2].

Ultrasonic techniques are complementary to other physical methods used in surgery, therapy and diagnosis, based on the properties of longitudinal waves in the frequency range 1-15 MHz Ultrasonic waves travel at similar velocities (about 1500 m s^{-1}) in most biological tissues, and are absorbed at a rate of about 1 dB cm^{-1} MHz^{-1}. Absorption occurs mainly due to relaxation processes. It leads to thermal effects in biological systems. Mechanical effects, such as streaming and cavitations, are also important in certain situations, particularly at low frequencies. Highly focused ultrasound is used in neurosurgery; it is the only method for producing trackless damage deep in the brain. In vestibular surgery, ultrasonic irradiation is used routinely for the treatment of Ménière's disease (endolymphatic hydrops, is a disorder of the inner ear that can affect hearing and balance to a varying degree.); it can alleviate the symptoms without damage to the hearing. Therapeutic applications include the treatment in physiotherapy of various soft-tissue ailments, and the production of aerosols for inhalation. The examination of soft tissues is possible both by pulse-echo and continuous-wave techniques. Ultrasonic diagnosis provides information about the position and extent of characteristic impedance discontinuities; this information cannot be obtained directly by any other method. One- and two-dimensional displays, and time-position wave forms, are produced by pulse-echo techniques. Continuous-wave techniques include those based on the Doppler frequency shift of ultrasound reflected by moving structures.

2. Applications of Ultrasound in Medical Science:

2.1 Imaging and Diagnosis: Identification and Detection
From the introducing of the processing of the signals of gray scale in 1974 B-mode of the sonography became the widely accepted method. The progress in the forming of the transducers has led to better space resolution and the imaging of very small structures in the abdomen (0.5-1 cm). The development of real-time system led to, even, to the possibility of the continued visualization or the ultrasound fluoroscopy [1]. In the ultrasound diagnostics can be differed two techniques: transmission and reflection.

Transmission technology is based on distinguishing the tissues with different absorbance of ultrasound. Due to uneven absorption of ultrasound images provides internal structure that consists of a mosaic of lighter and darker places. Reflection technology (echo) registers the pulse is reflected from the boundary of two tissues with different acoustic resistance. The technique is based on principle of functioning sonar ("Sonar Navigation and Ranging"). The frequencies can be anywhere between 2 and 18 MHz's. This focusing produces an arc-shaped sound wave from the face of the transducer. The wave travels into the body and comes into focus at a desired depth. Newer technology transducers use phased array techniques to enable the sonographic machine to change the direction and depth of focus. Almost all piezoelectric transducers are made of ceramic [1, 2]

[1]To generate a 2 D-image, the ultrasonic beam is swept. A transducer may be swept mechanically by rotating or swinging. Or a 1D phased array transducer may be use to sweep the beam electronically. The received data is processed and used to construct the image. The image is then a 2D representation of the slice into the body. 3D images can be generated by acquiring a series of adjacent 2D images. However, since the mechanical scanning is slow, it is difficult to make 3D images of moving tissues. Recently, 2D phased array transducers that can sweep the beam in 3D have been developed. These can image faster and can even be used to make live 3D images of a beating heart.

[1]Four different modes of ultrasound are used in medical imaging [1, 2, 3]. In A-mode a single transducer scans a line through the body with the echoes plotted on screen as a function of depth. Therapeutic ultrasound aimed at a specific tumor or calculus is also A-mode, to allow for pinpoint accurate focus of the destructive wave energy. In B-mode ultrasound, a linear array of transducers simultaneously scans a plane through the body that can be viewed as a two-dimensional image on screen. In M-mode (M stands for motion) a rapid sequence of B-mode scans whose images follow each other in sequence on screen enables doctors to see and measure range of motion, as the organ boundaries that produce reflections move relative to the probe.

1.1.1 Colour Doppler Imaging and Doppler Tomography

In Doppler mode, the Doppler effect is used in measuring and visualizing blood flow. It employs the Doppler effect to assess whether structures (usually blood) are moving towards or away from the probe, and its relative velocity. By calculating the frequency shift of a particular sample volume, for example a jet of blood flow over a heart valve, its speed and direction can be determined and visualized. This is particularly useful in cardiovascular studies (sonography of the vasculature system and heart) and essential in determining reverse blood flow in the liver vasculature in portal hypertension. The Doppler information is displayed graphically using spectral Doppler, or as an image using color Doppler (directional Doppler) or power Doppler (non directional Doppler). Difference in transmitted and received frequency is called Doppler shift.

Ultrasonic colour Doppler is an imaging technique that combines anatomical information derived using ultrasonic pulse-echo techniques with velocity information derived using ultrasonic Doppler techniques to generate colour-coded maps of tissue velocity superimposed on grey-scale images of tissue anatomy. The most common use of the technique is to image the movement of blood through the heart, arteries and veins, but it may also be used to image the motion of solid tissues such as the heart walls. Colour Doppler imaging is now provided on almost all commercial ultrasound machines, and has been found to be of great value in assessing blood flow in many clinical conditions. It also has a number of weaknesses, perhaps the greatest being that in conventional systems, the velocities measured and thus displayed are the components of the flow velocity directly towards or away from the transducer, while ideally the method would give information about the magnitude and direction of the three-dimensional flow vectors. It is safe, fast and interactive systems for studying all parts of the human circulation. The new methods for vector velocity imaging are on the threshold of being introduced, will add new information to the field allowing the detailed study of complex flow, and they will make the imaging easier as they are angle-independent. There is a real need for three-dimensional vector velocity estimation and the frame rate needs to be increased to the 100 Hz range to study complex flow and vortex formation in the heart and other complex anatomical structures [4]

Considering the pulse-echo principle, it is natural to think that continuous wave (CW) US is not suitable for imaging owing to its long (or its, effectively, infinitely long) pulse duration [5, 6]. Thus, the Doppler phenomenon associated with CW has generally been limited to the detection of movement of tissue, such as blood flow [7]. However, it is possible to apply CW to generate US images using a special case of the Doppler phenomenon that is caused by relative movement between the target and the probe. This US imaging modality is termed the 'Doppler tomography' (DT) method [8]; it should not be confused with another class of tomography method called ultrasonic computed tomography (UCT) [9, 10], which uses pulse (transmission mode) or pulse-echo (reflection mode) US. In ultrasonic DT, the tissue to be imaged is moved with respect to an ultrasonic beam and reflecting and scattering targets within the tissue return echoes that are correspondingly Doppler-shifted in frequency. A tomographic method has been used to detect the existence of flowing fluid in a phantom (a physical model simulating relevant anatomical features); however, neither the phantom nor the transducer was moved to cause the Doppler effect and, therefore, only the fluid flow was detected [11]. Ultrasonic imaging using the Doppler effect caused by a linearly moving transducer has also been demonstrated [12]. The idea of rotating the targets to cause the ultrasonic Doppler effect for spatial imaging was first proposed more than 30 years ago [13], but was not realized until we constructed a system for incoherent CW ultrasonic DT. Thus, this is different from the established method of Doppler imaging in which the Doppler effect is caused by physiological movement of the blood or tissues [5].

DT is different from conventional UCT in that DT uses CW while UCT uses pulsed US. There are two types of UCT: transmission and reflection. The former is used to determine the attenuation and speed of sound in tissues. The latter is used to detect the reflectivity of targets. DT only detects reflectivity. It also needs relative motion between probe and tissue while UCT does not. The development of DT is still in its early stages. In medical imaging, three-dimensional images can provide extra information that cannot be revealed by two-dimensional images. Often, three-dimensional images are formed by stacking parallel two-dimensional images in a volumetric dataset. Three-dimensional DT images can be created by translating the probe along the direction of the axis of rotation [5]. An alternative is first to rotate the probe around the rotation axis of the target and then to move the probe in a plane containing the rotation axis of the target but at an angle to it.

1.1.2 Properties of Tissues

Two decades ago, only acoustic waves used for imaging biological structures were ultrasonic compressional (or longitudinal) waves. In the 1990s, a new acoustic imaging technology started to emerge that was based on shear (or transverse) acoustic waves. Compressional wave speed is related to the bulk modulus of the tissue, whereas shear wave speed is related to the shear modulus. Compressional wave speed does not vary significantly for biological tissues compared with the variation of the shear wave velocity in the same tissues [13]. For this reason, elasticity imaging, which is targeted at imaging the shear modulus of tissue, has a wide dynamic range that can be exploited.

Shear wave speeds are sensitive to tissue structure. Shear material properties provides large potential for characterizing different types of tissue, normal or pathologic. There is a large frequency range over which shear wave measurements can be made, providing possibilities to evaluate soft tissue shear wave speed dispersion. This dispersion, whether caused by viscoelasticity or geometry or a combination of these two factors, can be used to sensitively evaluate material properties of the studied tissue. Also, parameters such as tissue anisotropy, viscosity and non-linearity can be characterized using shear waves. These parameters may serve as interesting biomarkers that could yield important diagnostic information [13]. Shear acoustic imaging is still a young imaging modality that will continue to develop and has substantial potential for characterizing different soft tissues for clinical diagnosis.

Conventional diagnostic ultrasound images portray differences in the acoustic properties of soft tissues, whereas ultrasound-based elasticity images describe differences in the elastic properties of soft tissues (i.e. stiffness, viscosity). The benefit of elasticity imaging lies in the fact that many soft tissues can share similar ultrasonic echogenicities, but may have different mechanical properties that can be used to clearly visualize normal anatomy and mark out pathological lesions. Acoustic radiation force-based elasticity imaging methods use acoustic radiation force to transiently deform soft tissues, and the dynamic displacement response of those tissues is measured ultrasonically and is used to estimate the tissue's mechanical properties [14]. Both qualitative images and quantitative elasticity metrics can be reconstructed from these measured data, providing complimentary information to both diagnose and longitudinally monitor disease progression. Clinicians are beginning to characterize tissue stiffness as a diagnostic metric.

The fusion of nonlinear and swept frequency calibration approach provided sensitivity versus frequency response of the probes in the frequency range up to 100 MHz. The availability of hydrophone probes calibrated in such wide frequency range is crucial for further development of ultrasound imaging performed at the frequencies that would produce images comparable with those achievable using magnetic resonance imaging (MRI). This is essential as the diagnostic power of ultrasound modality and its clinical importance critically depends on the image quality. In general, optimization of the equipment used in biomedical ultrasonics requires knowledge of the dependence of the relevant acoustic field parameters, including pressure-time waveform and the treated or diagnosed tissue [15].

Importance of HF ultrasound imaging using frequencies beyond 20 MHz is growing in a variety of areas from basic scientific research, through drug development, to medical diagnosis and non-destructive testing of materials. Applications of clinical HF ultrasound in dermatology, odontology and ophthalmology are also rapidly increasing. Ultrasound biomicroscopy implemented at the frequencies above 100 MHz is used to examine specific properties of the tissue and membranes, and to study life cycles of cells. Submillimeter resolution ultrasound combined with contrast agents also proved to be suitable as a tool for monitoring of structural changes in cells evoked by extraneous stimulants such as chemo- or radiation therapy. HF elastography can be used in detecting tumors in soft tissue, differentiating malignant and gentle tumors, and in detection and characterization of vulnerable plaque [16]. Most likely ultrasound based images will be combined or fused with the images obtained using other modality, such as light.

Research into possibilities of employing multimodality imaging will also increase and it is possible that ultrasound scans could be combined with the functional information obtained from micro PET scanner to optimize cancer detection. It is also worthwhile to note that expanding clinical applications of HF ultrasound increase the need for quantitative measurements of ultrasound fields beyond 20 MHz. Such probes will be miniaturized by using fiber optic technology and once fully optimized they will exhibit uniform frequency response in the whole 100 MHz bandwidth and behavior close to that of ideal point receiver.

The high frequency 'micro-ultrasound' has steadily evolved as a rapid, comparatively inexpensive imaging tool for studying normal development and models of human disease in small animals. One of the fundamental barriers to this development was the technological hurdle associated with high-frequency array transducers. Recently, new approaches have enabled the upper limits of linear and phased arrays to be pushed from about 20 to over 50 MHz enabling a broad range of new applications in cancer, and cardiovascular disease [17].

Development of an integrated platform for high-frequency photoacoustic imaging has recently been reported by Needles et al. [18]. This technology may impact cancer research by providing a non-invasive means of evaluating tumour oxygenation. Through the development of nanoparticle-based contrast agents, photoacoustics may also allow the extracellular compartment to be probed. Optical absorption spectroscopy of the tumour microenvironment may allow other new dimensions of tumour growth to be assessed. Shear modulus imaging represents another opportunity to probe fluctuations of elastic properties in tumours as they grow and are treated [17]. The ability to perform this type of imaging at much higher frequencies may reveal new physical properties of tumour tissue. Finally, it should be noted that micro-ultrasound, having undergone dramatic expansion in the field of preclinical imaging, is now ripe to be exploited in clinical applications. Already efforts are underway to use the technology in prostate imaging, neonatal imaging, skin and ocular imaging and a wide range of intraluminal imaging applications.

1.1.3 Liver Fibrosis and Liver Cirrhosis: ARFI

Acoustic radiation force impulse (ARFI) elastography is the most feasible shear wave elastographic method for assessment of liver fibrosis, especially in obese patients, whereas TE and SSI are similar with respect to rate of reliable liver stiffness (LS) measurements. With TE as the reference method for liver fibrosis evaluation, ARFI and SSI had similar rates accuracy in diagnosing significant fibrosis and liver cirrhosis [19].

1.1.4 Transoesophageal Echo Cardiography:

The transoesophageal echo cardiography (TEE) opened the window in the diagnostic imaging in the field of the cardiography, card surgery and anesthesia. Using TEE in 2-D mode, the anesthesiologist can monitor the heart movements, and cardiac surgeon will become the valuable information about the heart condition after the critical surgical procedure [2].

1.2 Respiratory variation

Respiratory variation in the inferior vena cava (IVC) has been extensively studied with respect to its value in predicting fluid responsiveness, but the results are conflicting. Study indicates that IVC measured with point-of-care ultrasonography is of great value in predicting fluid responsiveness, particularly in patients on controlled mechanical ventilation and those resuscitated with colloids [20].

1.3 Vulnerable Plaque Identification by IVPA Imaging:

The vulnerable atherosclerotic plaque is believed to be at the root of the majority of sensitive coronary events. Even though the exact origins of plaque vulnerability remain elusive, the thin-cap fibroatheroma, characterized by a lipid-rich necrotic core covered by a thin fibrous cap, is considered to be the most prominent type of vulnerable plaque. No clinically available imaging technique can characterize atherosclerotic lesions to the extent needed to determine plaque vulnerability prognostically. Intravascular photoacoustic imaging (IVPA) has the potential to take a significant step in that direction by imaging both plaque structure and composition. IVPA is a natural extension of intravascular ultrasound that adds tissue type specificity to the images. IVPA utilizes the optical contrast provided by the differences in the absorption spectra of plaque components to image composition. By simultaneously displaying plaque morphology and composition, IVPA can provide a powerful prognostic marker for disease progression, and as such has the potential to transform the current practice in percutaneous coronary intervention [21].

1.4 Plantar Fasciitis

Plantar fasciitis (PFS) is one of the most common causes of heel pain, estimated to affect 10% of the general population during their lifetime. Ultrasound (US) imaging technique is an accurate, reliable and non-invasive imaging technique to assess plantar fascia (PF) thickness, monitor the effect of different interventions and guide therapeutic interventions in patients with PFS [22].

1.5 Thermal Strain Imaging

A new ultrasonic imaging technique, Thermal strain imaging (TSI), or temporal strain imaging is an ultrasound application that exploits the temperature dependence of sound speed to create thermal (temporal) strain images. Phantom, ex vivo, and in vivo results illustrated two potential clinical applications. In the first, TSI can resolve water-based and lipid-based tissue at contrast and spatial resolution appropriate for arterial studies. In particular, it has the potential to distinguish a lipid-laden pool from the arterial vascular wall within a carotid plaque. A major obstacle for any in vivo application such as plaque characterization in the carotid is tissue motion, including respiratory and cardiac motion. Respiratory motion can be eliminated or minimized since TSI can be achieved within 2–3 s while the subject holds his/ her breath [23].

A number of invasive and non-invasive imaging techniques are presently available to assess atherosclerotic vessels, these are ECG, acoustic radiation force impulse (ARFI), X-ray angiography, IVUS, optical coherence tomography (OCT), intravascular MRI, Optical frequency domain imaging (OFDI), B-mode US, X-ray CT and MRI. All these techniques hold promise to detect high-risk plaque in coronary arteries, while certain limitations apply. TSI has the clear potential to become part of an integrated US examination to characterize plaque in peripheral vessels such as the carotid artery. A second potential clinical application of TSI is to monitor the progression of RF ablation in the myocardium. Using an intra cardiac catheter integrating RF ablation delivery and real-time US imaging, TSI data can be continuously recorded during the ablation procedure. Irreversible injury to tissue and a complete heart block occur at around 48–50 ^{o}C. The speed of sound for most water-bearing tissue increases with temperature. However, at temperatures above about 50^{o}C, there is no further increase in the sound speed. Using these two properties, a potential tool to optimize therapy and detect the moment when clinically significant tissue damage occurs is possible using the reduced slope in the thermal strain as a function of heating time [23].

2. Advanced Applications in Medicinal, Therapeutic and Surgery

2.1 Gravity-defying Ultrasonic tweezers

On 3 June 2014 Professor Martyn Hill Professor of Electromechanical Systems, Dr Peter Glynne-Jones Researchers from the University of Southampton have helped to develop pioneering ‘tweezers’ that use ultrasound beams to grip and manipulate tiny clusters of cells, which could lead to life-changing medical advances, such as better cartilage implants that reduce the need for knee replacement operations [24]. Using ultrasonic sound fields, cartilage cells taken from a patient’s knee can be levitated for weeks in a nutrient-rich fluid. This means the nutrients can reach every part of the culture's surface and, combined with the stimulation provided by the ultrasound, enables the cells to grow and to form better implant tissue than when grown on a glass petri dish.

By holding the cells in the required position firmly but gently, the tweezers can also mould the growing tissue into exactly the right shape so that the implant is truly fit-for-purpose when inserted into the patient's knee. Over 75,000 knee replacements are carried out each year in the UK; many could be avoided if cartilage implants could be improved [24].

2.2 Odor Representation in Brain

On July 15, 2014 in *NeuroImage* , published a new ultrasound imaging technique has provided the first ever in vivo visualization of activity in the piriform cortex of rats during odor perception. This deep-seated brain structure plays an important role in olfaction, and was inaccessible to functional imaging until now. This work also sheds new light on the still poorly known functioning of the olfactory system, and notably how information is processed in the brain. This study is the result of collaboration between the team led by Mickael Tanter at the Institute Langevin [25].

2.3 Newly Patented Device for Treatment of Stroke Patients

A new device developed on 21st August, 2014 by a physician at the University of Arkansas for Medical Sciences and a researcher at the University of Arkansas at Little Rock could soon be available to treat stroke more effectively. The Clot Bust ER® fits on the head like a halo and delivers therapy to quickly bust clots that cause stroke. It was developed by William Culp, M.D., professor of radiology, surgery and neurology and vice chairman of research at UAMS, and Doug Wilson, assistant director at the Graduate Institute of Technology at UALR [26].

While looking into the treatment to dissolve clots in blood vessels, Culp realized one problem is getting the ultrasound to operate through the skull. Ultrasound can be delivered anywhere in a patient's body unless the waves hit something hard like bone or something very soft, like air. The Clot Bust ER® has 16 transducers scattered around the inside -- designed to line up with the thin points in the skull: the temples and the foramen magnum in the base of the skull. This allows the ultrasound waves to move through the brain without interruption. After the patient is administered an IV containing t-PA, the circular device is placed onto the patient's head like a sports visor or halo. "The idea is to deliver ultrasound wherever the clot is and where the IV t-PA is working," Culp said. "It makes t-PA work better -- improving the clot-busting drug by 40 or 50 percent. It's like taking a cooking pot and stirring it. The ultrasound stirs the drug around, making it work better [26].

2.4 Non-invasive Technique for Drug Delivery - Penetrating the Blood-Brain Barrier

On 14th August, 2014, new technique developed by Elisa Konofagou, professor of biomedical engineering and radiology at Columbia University School of Engineering and Applied Science , has demonstrated for the first time that the size of molecules penetrating the blood-brain barrier (BBB) can be controlled using acoustic pressure -- the pressure of an ultrasound beam -- to let specific molecules through. The study was published in the July issue of the *Journal of Cerebral Blood Flow & Metabolism* [27]. This is an important breakthrough in getting drugs delivered to specific parts of the brain precisely, non-invasively, and safely, and may help in the treatment of central nervous system diseases like Parkinson's and Alzheimer's. Most small -- and all large -- molecule drugs do not currently penetrate the blood-brain barrier that sits between the vascular bed and the brain tissue. Parkinson's disease would benefit by delivery of therapeutic molecules to the neurons so as to impede their slow death. But because of the virtually impermeable barrier, these drugs can only reach the brain through direct injection and that requires anesthesia and drilling the skull while also increasing the risk of infection and limiting the number of sites of injection, and transcranial injections rarely work -- only about one in ten is successful.

Focused ultrasound in conjunction with microbubbles -- gas-filled bubbles coated by protein or lipid shells -- continues to be the only technique that can permeate the BBB safely and non-invasively. When microbubbles are hit by an ultrasound beam, they start oscillating and, depending on the magnitude of the pressure, continue oscillating or collapse. While researchers have found that focused ultrasound in combination with microbubble cavitation can be successfully used in the delivery of therapeutic drugs across the BBB, almost all earlier studies have been limited to one specific-sized agent that is commercially available and widely used clinically as ultrasound contrast agents. Konofagou and her team were convinced there was a way to induce a size-controllable BBB opening, enabling a more effective method to improve localized brain drug delivery. Higher acoustic pressures led to larger molecules accumulating into the hippocampus as confirmed by fluorescence imaging. This demonstrated that the pressure of the ultrasound beam can be adjusted depending on the size of the drug that needs to be delivered to the brain: all molecules of variant sizes were able to penetrate the opened barrier but at distinct pressures, i.e., small molecules at lower pressures and larger molecules at higher pressures [27].

2.5 Bone Tumor Incisionless Surgery

On 6th August, 2014, the *Focused Ultrasound Foundation* has declared the Patient at The Hospital for Sick Children (Sick Kids) is the first child in North America to have undergone a specialized procedure that uses ultrasound and magnetic resonance imaging (MRI) to destroy a tumor in his leg without piercing the skin [28]. Doctors used an MRI to guide high-intensity ultrasound waves to destroy a benign bone tumor called osteoid osteoma. The lesion had caused 16-year-old Jack Campanile, a Canadian child, excruciating pain for a year prior to the July 17 procedure. By the time he went to bed that night, the athletic teen experienced complete pain relief.

2.6 New Hand-held Device for Deeper Melanoma Imaging

Melanoma is the deadliest form of skin cancer, causing more than 75 percent of skin-cancer deaths. It is the fifth most common cancer type in the United States, and incidence rates are rising faster than those of any other cancer. The thicker the melanoma tumor, the more likely it will spread and the deadlier it becomes. Now, a team of researchers has developed a new hand-held device that uses lasers and sound waves that may change the way doctors treat and diagnose melanoma. The tool is ready for commercialization and clinical trials [29].

A new hand-held device that uses lasers and sound waves may change the way doctors treat and diagnose melanoma, according to declaration of a team of researchers from Washington University in St. Louis (The Optical Society) on 6th August, 2014. The instrument, described in a paper published in The Optical Society's (OSA) journal *Optics Letters*, is the first that can be used directly on a patient and accurately measure how deep a melanoma tumor extends into the skin, providing valuable information for treatment, diagnosis or prognosis [29].

Recently, researchers including Wang have applied an approach called photoacoustic microscopy, which can accurately measure melanoma tumors directly on a patient's skin -- thus allowing doctors to avoid uncertainty in some circumstances. The technique relies on the photoacoustic effect, in which light is converted into vibrations. In the case of the new device, a laser beam shines into the skin at the site of a tumor. Melanin, the skin pigment that's also in tumors, absorbs the light, whose energy is transferred into high-frequency acoustic waves. Unlike light, acoustic waves don't scatter as much when traveling through skin. Tumor cells will produce more melanin than the surrounding healthy skin cells, and as a result, the acoustic waves can be used to map the entire tumor with high resolution. The device has a detector that can then turn the acoustic signal into a three-dimensional image on a screen. It can measure a tumor's entire volume -- something that's never been possible with melanoma. If researchers can determine how the volume relates to cancer outcomes, then this tool could give doctors a new type of measurement for diagnosis and prognosis.

2.7 Transcranial Ultrasound Therapy: Brain Tumours and Targeted Drug Delivery

A recent study completed at the University of Eastern Finland on provides new information on the limitations and potential new directions for the future development of transcranial ultrasound therapy. Active research is taking place in the field of transcranial ultrasound therapy, which in the future can potentially be applied to the treatment of brain tumours and targeted drug delivery [30]. The therapy modality has already been successfully applied to the treatment of neuropathic pain disorder and essential tremors. The benefits of transcranial ultrasound therapy include minimal invasiveness, as the treatment is delivered to the brain by transmitting ultrasound through the intact skull of the patient. The study focuses on two issues that may potentially limit the applicability of transcranial ultrasound: skull-base heating and formation of standing-waves. As the ultrasound beam encounters the skull bone, part of the beam's energy is transferred into the skull as heat. In the study, it was found that the heating of the skull-base during transcranial ultrasound therapy can result in hazardous temperature elevations when the sonications are performed close to the skull-base. Three new methods to counteract this potentially hazardous phenomenon were developed in the study. The formation of standing waves is greatly reduced when specifically designed large-area ultrasound transducers are used [30].

2.8 Delivering Chemo Drugs on Cue: Drug Delivery

Led by David J. Mooney, Ph.D., a Core Faculty member at Harvard's Wyss Institute for Biologically Inspired Engineering and the Robert P. Pinkas Family Professor of Bioengineering at the Harvard School of Engineering and Applied Sciences (SEAS) on 23rd June, 2014, the team loaded a biocompatible hydrogel with a chemotherapy drug and used ultrasound to trigger the gel to release the drug

[31]. Like many other injectable gels that have been used for drug delivery for decades, this one gradually releases a low level of the drug by diffusion over time. To temporarily increase doses of drug, scientists had previously applied ultrasound -- but that approach was a one-shot deal as the ultrasound was used to destroy those gels. This gel was different. The team used ultrasound to temporarily disrupt the gel such that it released short, high-dose bursts of the drug -- akin to opening up a floodgate. But when they stopped the ultrasound, the hydrogels self-healed. By closing back up, they were ready to go for the next "on demand" drug burst -- providing an innovative way to administer drugs with a far greater level of control than possible before. That's not all. The team also demonstrated in lab cultures and in mice with breast cancer tumors that the pulsed, ultrasound-triggered hydrogel approach to drug delivery was more effective at stopping the growth of tumor cells than traditional, sustained-release drug therapy.

2.9 Using bubbles to reveal fertility problems

Doctors in University of California, San Diego Health Sciences are the first fertility specialists in the county to use a new ultrasound technique to assess fallopian tubes by employing a mixture of saline and air bubbles that is less painful, avoids X-ray exposure and is more convenient to patients during an already vulnerable time. Using the technique, the physician delivers the mixture of saline and air bubbles into the uterus through a small catheter, which then flows into the fallopian tubes. Under ultrasound, the air bubbles are highly visible as they travel through the tubes, allowing the physician to determine if a blockage exists [32].

2.10Listening to Cells: Scientists Probe Human Cells

On 1st February, 2013 the Biophysical Society declared that the researchers have developed a new non-contact, non-invasive tool to measure the mechanical properties of cells at the sub-cell scale. Now scientists have developed a way to use sound to probe tissue on a much tinier scale. Researchers from the University of Bordeaux in France deployed high-frequency sound waves to test the stiffness and viscosity of the nuclei of individual human cells. The scientists predict that the probe could eventually help answer questions such as how cells adhere to medical implants and why healthy cells turn cancerous [33]. Audoin and his colleagues, in collaboration with a research group in biomaterials led by Marie-Christine Durrieu from the Institute of Chemistry & Biology of Membranes & Nano-objects at Bordeaux University, adapted pico second ultrasonics to study living cells. They grew cells on a metal plate and then flashed the cell-metal interface with an ultra-short laser pulse to generate high-frequency sound waves. Another laser measured how the sound pulse propagated through the cells, giving the scientists clues about the mechanical properties of the individual cell components. They use gigahertz waves, so can probe objects on the order of a hundred nanometers [33].

2.11New Device in Detecting Risk for Heart Attack, Stroke

A new ultrasound device that could help identify arterial plaque that is at high risk of breaking off and causing heart attack or stroke has been developed by researchers. The prototype device has performed well in laboratory testing, but the researchers say they are continuing to optimize the technology. They hope to launch pre-clinical studies in the near future. There are two ultrasound techniques that can help identify vulnerable plaques, but both depend on the use of contrast agents called "microbubbles." The first technique is to identify "vasa vasorum" in arteries. These are clusters of small blood vessels that often infiltrate arterial plaque, and which are considered indicators that a plaque is vulnerable. When microbubbles are injected into an artery, they follow the flow of the blood. If vasa vasorum are present, the microbubbles will flow through these blood vessels as well, effectively highlighting them on ultrasound images. The second technique is called molecular imaging, and relies on the use of "targeted" microbubbles. These microbubbles attach themselves to specific molecules that are more likely to be found in vulnerable plaques, making the plaques stand out on ultrasound images. The researchers have developed a dual-frequency intravascular ultrasound transducer which transmits and receives acoustic signals. Operating on two frequencies allows to do everything the existing intravascular ultrasound devices can do, but also makes it much easier for us to detect the contrast agents -- or microbubbles -- used for molecular imaging and vasa vasorum detection [34].

2.12High Resolution Imaging to Visualize a Single Cell

SAIJO, Yoshifumi , Professor (PhD (Medicine)) Biomedical Imaging Laboratory, Graduate School of Biomedical Engineering has been reported High-resolution in vivo biological imaging is non-invasively obtained with high frequency ultrasound. He and his group have developed some ultrasound microscope systems which realized the resolution of 15-micron with 100 MHz and resolution to visualize a single cell with GHz range ultrasound. Ultrasonic imaging provides not only tissue morphology but also tissue elasticity. They have developed high frequency array transducer for easier [35].

3. Risks and Side-effects

Safety Considerations

It is essential to maintain caution to ensure the continued safe use of ultrasound. Ultrasound examinations should only be performed by competent personnel who are trained and updated in safety matters. It is also important that ultrasound devices are appropriately maintained. Ultrasound produces heating, pressure changes and mechanical disturbances in tissue. Diagnostic levels of ultrasound can produce temperature rises that are hazardous to sensitive organs and the embryo / foetus. The thermal index (TI) is an on-screen guide to the user of the potential for tissue heating. The mechanical index (MI) is an on-screen guide of the likelihood and magnitude of non thermal effects. Users should regularly check both indices while scanning and should adjust the machine controls to keep them as low as reasonably achievable (ALARA principle). Where low values cannot be achieved, examination times should kept as short as possible [36].

Spectral pulse wave Doppler and Doppler imaging modes (colour flow imaging and power Doppler imaging) in particular can produce more tissue heating and hence higher TI values, as can B mode techniques involving coded transmissions. Tissue harmonic imaging mode can sometimes involve higher MI values. 4D scanning (real-time 3D) involves continuous exposure and users should guard against the temptation to prolong examination [36].

The embryo/foetus in early pregnancy is known to be particularly sensitive. Care should be taken to limit the exposure time and the Thermal and Mechanical Indices to the minimum commensurate with an acceptable clinical assessment. Temperature rises are likely to be greatest at bone surfaces and adjacent soft tissues. With increasing mineralisation of foetal bones, the possibility of heating sensitive tissues such as brain and spinal cord increases. Extra caution is advised when scanning such critical foetal structures, at any stage in pregnancy. Doppler ultrasound examinations should not be used routinely in the first trimester of pregnancy. Particular care should be taken to reduce the risk of thermal and non-thermal effects during investigations of the eye and when carrying out neonatal cardiac and cranial investigations [36].

Ultrasound contrast agents (UCA) usually take the form of stable gas filled microbubbles, which can potentially produce cavitations or micro streaming, the risk of which increases with MI value. Data from small animal models suggest that micro vascular damage or rupture is possible. Caution should be considered for the use of UCA in tissues where damage to microvasculature could have serious clinical implications, such as in the brain, the eye, and the neonate. As in all diagnostic ultrasound procedures, the MI and TI values should be continually checked and kept as low as possible. It is possible to induce premature ventricular contractions in contrast enhance [36].

Ultrasonography is generally considered a safe imaging modality. Diagnostic ultrasound studies of the fetus are generally considered to be safe during pregnancy. This diagnostic procedure should be performed only when there is a valid medical indication, and the lowest possible ultrasonic exposure setting should be used to gain the necessary diagnostic information under the "as low as reasonably practicable" or ALARP principle.

World Health Organizations technical report series 875 (1998) supports that ultrasound is harmless. Although there is no evidence ultrasound could be harmful for the fetus, US Food and Drug Administration views promotion, selling, or leasing of ultrasound equipment for making "keepsake fetal videos" to be an unapproved use of a medical device. Medical ultrasonography should not be performed without a medical indication to perform it. Overuse of ultrasonography is reported in the United States, especially as routine screening for deep vein thrombosis after orthopedic surgeries in patients who are not at heightened risk for having that condition.

A study at the Yale School of Medicine published in 2006 found a small but significant correlation between prolonged and frequent use of ultrasound and abnormal neuronal migration in mice [37]. A study performed in Sweden in 2001 has shown that subtle effects of neurological damage linked to ultrasound were implicated by an increased incidence in left-handedness in boys (a marker for brain problems when not hereditary) and speech delays [38]. A later study, however, performed on a larger sample of 8865 children, has established a statistically significant, albeit weak association of ultrasonography exposure and being non-right handed later in life [39].

4. Weaknesses and Limitations

Sonographic devices have trouble penetrating bone. For example, sonography of the adult brain is very limited though improvements are being made in transcranial ultrasonography. Sonography performs very poorly when there is a gas between the transducer and the organ of interest, due to the extreme differences in acoustic impedance. For example, overlying gas in the gastrointestinal tract often makes ultrasound scanning of the pancreas difficult, and lung imaging is not possible (apart from demarcating pleural effusions). Even in the absence of bone or air, the depth penetration of ultrasound may be limited depending on the frequency of imaging. Consequently, there might be difficulties imaging structures deep in the body, especially in fat patients. Body habitus has a large influence on image quality. Image quality and accuracy of diagnosis is limited with fat patients, overlying subcutaneous fat attenuates the sound beam and a lower frequency transducer is required (with lower resolution)

The method is operator-dependent. A high level of skill and experience is needed to acquire good-quality images and make accurate diagnoses. There is no scout image as there is with CT and MRI. Once an image has been acquired there is no exact way to tell which part of the body was imaged.

Important role in the detail and accuracy of ultrasound plays distinguishing details. Discrimination of an ultrasonic device can be defined as the minimum distance of two reflectors in the body that is on the screen can be recognized as separate. Resolution can be divided into Lateral (sideways) and Axial (depth). Lateral resolution depends on the thickness of the beam. At higher frequencies it is easier to achieve narrow beam, but the penetration is reduced. In examination of the children are used frequency 5-7 MHz, while in adults 3-5 MHz. If we work with the reduced sensitivity of the device, then the weak reflectors (parenchyma) lose the pictures, but the lateral resolution for the remaining, stronger, reflectors is better. Axial resolution is much better than regular lateral also for display of thin structures (e.g. thin blood vessels) the probe should be always oriented to the vessels so that blood flow across the ultrasound beam. At present conventional ultrasonic device to create images we are using only the amplitude (intensity) response [2].

The obesity and muscle atrophy mainly increase the number of reflective interfaces not only leading to more echoes but also decreasing incident sound available to penetrate deeper tissues, such as nerves, vessels, or other targeted structures.

Among the major US innovations of recent years, 3D US is the ideal tool to avoid the limitations with traditional US. However, many studies are required to ascertain its utility in the imaging of nerve structures. [40]

Clinical experience with 3D ultrasound has already demonstrated the clear advantages it offers both for the diagnosis of disease and in providing image guidance for minimally invasive therapy. Technical advances will improve 3D imaging even further, making it a routine tool. Although advances are required in both 3D visualization software and hardware, the potential for innovation is clearly present. Based on the pace of development over the past 5 years, many major advances can be anticipated over the next 5 years, leading to improvements in existing applications and to the development of newapplications in a wide variety of medical disciplines. [41]

5. Strengths

- It images muscle, soft tissue, and bone surfaces very well and is particularly useful for delineating the interfaces between solid and fluid-filled spaces.
- It renders "live" images, where the operator can dynamically select the most useful section for diagnosing and documenting changes, often enabling rapid diagnoses. Live images also allow for ultrasound-guided biopsies or injections, which can be cumbersome with other imaging modalities.
- It shows the structure of organs.
- It has no known long-term side effects and rarely causes any discomfort to the patient.
- Equipment is widely available and comparatively flexible.
- Small, easily carried scanners are available; examinations can be performed at the bedside.
- Relatively inexpensive compared to other modes of investigation, such as computed X-ray tomography and MRI.
- Spatial resolution is better in high frequency ultrasound transducers than it is in most other imaging modalities.
- Through the use of an Ultrasound research interface, an ultrasound device can offer a relatively inexpensive, real-time, and flexible method for capturing data required for special research purposes for tissue characterization and development of new image processing techniques
- Most ultrasound scanning is noninvasive (no needles or injections).
- Occasionally, an ultrasound exam may be temporarily uncomfortable, but it is almost never painful.
- Ultrasound is widely available, easy-to-use and less expensive than other imaging methods.
- Ultrasound imaging is extremely safe and does not use any ionizing radiation.
- Ultrasound scanning gives a clear picture of soft tissues that do not show up well on x-ray images.
- Ultrasound is the preferred imaging modality for the diagnosis and monitoring of pregnant women and their unborn babies.

6. Conclusion

Diagnostic ultrasound is recognized as a safe, effective, and highly flexible imaging modality capable of providing clinically relevant information about most parts of the body in a rapid and cost-effective fashion. The ultrasonic imaging becomes as versatile and inexpensive reliable technique with much less limitation as compare to other invasive and non invasive techniques. Within half decade this imaging technology as never best before enters the medical science in the diagnosis of tissues and tumors of cancer and of other diseases. Not only limited for imaging but also it proves its main role in various treatments and surgery. Its remarkable role has been proved to destroy the tumors, in fertility problems in drug delivery in case of blood-brain barrier and in diagnosing liver fibrosis and liver cirrhosis. Also it is being used in joints and muscle pain relief and, in deeper melanoma imaging.

References

[1] Masic I, Ridjanovic Z, Pandza H, Masic I. Medical informatics. Avicena. Sarajevo, 2010: 416-430.

[2] Aladin Carovac, Fahrudin Smajlovic, Dzelaludin Junuzovic, “Application of Ultrasound in Medicine”AIM 2011; 19(3): 168-171 vol 19 no 3 SEPTEMBER 2011, doi: 10.5455/aim.2011.19.168-171

[3] Bijelic J, Cocic M. et al. Savremena dostignuca u tehnici i medicinskoj dijagnostici ugastroenterologiji.U: Prvo jugoslovensko savetovanje “Tehnikaimedicina”, održano u Beogradu 1985. godine, zbornik radova, knjiga I, Beograd, 1985: 41-70.

[4] David H. Evans, Jørgen Arendt Jensen and Michael Bachmann Nielsen,” Ultrasonic colour Doppler imaging” Interface Focus (2011) 1, 490–502 doi:10.1098/rsfs.2011.0017, Downloaded from rsfs.royalsocietypublishing.org on November 9, 2014

[5] Haidong-Dong Liang, Chun Sing Louis Tsui, Michael Halliwell and Peter N. T. Wells “Continuous wave ultrasonic Doppler tomography”, *Interface Focus* 2011 1, doi: 10.1098/rsfs.2011.0018, Downloaded from rsfs.royalsocietypublishing.org on November 9, 2014

[6] Taylor, K. J. W., Burns, P. N. & Wells, P. N. T. 1988 Clinical applications of Doppler ultrasound. New York, NY: Raven Press.

[7] Wells, P. N. T. & Skidmore, R. 1985 Doppler developments in the last quinquennium. Ultrasound Med. Biol. 11, 613–623. (doi:10.1016/0301-5629(85)90034-1)

[8] Liang, H. D., Halliwell, M.&Wells,P.N.T. 2001Continuous wave ultrasonic tomography. IEEE Trans. Ultrason. Ferroelectr. Freq. Control 48, 285–292. (doi:10.1109/58.896141)

[9] Greenleaf, J. F. & Bahn, R. C. 1982 Breast scanning with ultrasonic computer-assisted tomography. Ultrasound Med. Biol. 8, 453.

[10] Greenleaf, J. F., Gisvold, J. J. & Bahn, R. C. 1982 Computed transmission ultrasound tomography. Med. Prog. Technol. 9, 165–170.

[11] Greenleaf, J. F. & Ylitalo, J. 1986 Doppler tomography. In Proc. IEEE Ultrasonic Symp., Williamsburg, VA, 1719 November 1986, pp. 837–841.

[12] Nagai, K. & Greenleaf, J. F. 1990 Ultrasonic-imaging using the Doppler-effect caused by a moving transducer. Opt. Eng. 29, 1249–1254. (doi:10.1117/12.55709)
[13] Review: ARMEN P. SARVAZYAN, MATTHEW W. URBAN, and JAMES F. GREENLEAF, "ACOUSTIC WAVES IN MEDICAL IMAGING AND DIAGNOSTICS", Ultrasound in Med. & Biol., Vol. 39, No. 7, pp. 1133–1146, 2013, http://dx.doi.org/10.1016/j.ultrasmedbio.2013.02.006
[14] Mark L. Palmeri and Kathryn R. Nightingale, "Acoustic radiation force-based elasticity imaging methods" *Interface Focus* 2011 1, doi: 10.1098/rsfs.2011.0023 first published online 8 June 2011 Downloaded from rsfs.royalsocietypublishing.org on November 9, 2014
[15] Peter A. Lewin, "Nonlinear Acoustics in Ultrasound Metrology and other Selected Applications" Phys Procedia. 2010 January 1; 3(1): 17–23. doi:10.1016/j.phpro. 2010.01.004.
[16] Peter A. Lewin, "High frequency biomedical and industrial ultrasound applications", Proceedings of the International Congress on Ultrasonics, Vienna, April 9-13, 2007, Paper ID 1796, Session K02: Plenary, doi:10.3728/ICUltrasonics. 2007.Vienna.1796 _lewin_plenary.
[17] F. Stuart Foster, John Hossack and S. Lee Adamson, "Micro-ultrasound for preclinical imaging" *Interface Focus* 2011 1, doi: 10.1098/rsfs.2011.0037 first published online 8 June 2011, Downloaded from rsfs.royalsocietypublishing.org on November 9, 2014.
[18] Needles, A., Heinmiller, A., Ephrat, P., Bilan-Tracey, C., Trujillo, A., Theodoropoulos, C., Hirson, D. & Foster, F. S. In press. Development of a combined photoacoustic micro-ultrasound system for estimating blood oxygenation. In Proc. 2010 IEEE Ultrasonics Symp.
[19] IOAN SPOREA, SIMONA BOTA, ANA JURCHIS, ROXANA SIRLI, OANA GRADINARU-TASCAU, "ACOUSTIC RADIATION FORCE IMPULSE AND SUPERSONIC SHEAR IMAGING VERSUS TRANSIENT ELASTOGRAPHY FOR LIVER FIBROSIS ASSESSMENT" Ultrasound in Med. & Biol., Vol. 39, No. 11, pp. 1933–1941, 2013, http://dx. doi.org/10.1016/j.ultrasmedbio. 2013.05.003.
[20] ZHONGHENG ZHANG, XIAO XU, SHENG YE, and LEI XU, Ultrasound in Med. & Biol., Vol. 40, No. 5, pp. 845–853, 2014, http://dx.doi.org/10.1016/j.ultrasmedbio.2013.12.010
[21] KRISTA JANSEN, GIJS VAN SOEST, and ANTONIUS F. W. VAN DER STEEN, "INTRAVASCULAR PHOTOACOUSTIC IMAGING: A NEW TOOL FOR VULNERABLE PLAQUE IDENTIFICATION" Ultrasound in Med. & Biol., Vol. 40, No. 6, pp. 1037–1048, 2014, http://dx. doi.org/10.1016/ j.ultrasmedbio. 2014.01.008
[22] MOHAMMAD ALI MOHSENI-BANDPEI, MASOOMEH NAKHAEE, MOHAMMAD EBRAHIM MOUSAVI, "APPLICATION OF ULTRASOUND IN THE ASSESSMENT OF PLANTAR FASCIA IN PATIENTS WITH PLANTAR FASCIITIS: A SYSTEMATIC REVIEW", Ultrasound in Med. & Biol., Vol. 40, No. 8, pp. 1737–1754, 2014, http://dx.doi.org/10.1016/j.ultrasmedbio. 2014.03.001
[23] Chi Hyung Seo, Yan Shi, Sheng-Wen Huang, Kang Kim and Matthew O'Donnell, "**Thermal strain imaging: a review**"*Interface Focus* 2011 **1**, doi: 10.1098/rsfs.2011.0010 first published online 23 May 2011, Downloaded from rsfs.royalsocietypublishing.org on November 9, 2014.
[24] Professor Martyn Hill Professor of Electromechanical Systems, Dr Peter Glynne-Jones 3 June 2014, University of Southampton, "Southampton researchers help develop gravity-defying ultrasonic tweezers that could lead to life-changing medical advances"
[25] Mickael Tanter - Institut Langevin, (CNRS/INSERM/ESPCI ParisTech/UPMC/Université Paris Diderot) and Hirac Gurden (CNRS/Université Paris-Sud/Université Paris DiderotB.F. Osmanski, C. Martin, G. Montaldo, P. Lanièce, F. Pain, M. Tanter, H. Gurden, *NeuroImage*, 2014; 95: 176 DOI: 10.1016/j.neuroimage.2014.03.054, downloaded online from Science Daily.
[26] The Clot Bust ER® by William Culp, M.D., professor of radiology, surgery and neurology and vice chairman of research at UAMS, University of Arkansas for Medical Sciences and a researcher Doug Wilson, assistant director at the Graduate Institute of Technology at UALR, the University of Arkansas at Little Rock, downloaded online from Science Daily.
[27] Hong Chen, Elisa E Konofagou. **"**The size of blood–brain barrier opening induced by focused ultrasound is dictated by the acoustic pressure**."** *Journal of Cerebral Blood Flow & Metabolism*, 2014; 34 (7): 1197 DOI:10.1038/jcbfm.2014.71
[28] Dr. James Drake, Lead of CIGITI, Head of the Division of Neurosurgery and Senior Associate Scientist at SickKids, Centre for Image-Guided Innovation and Therapeutic Intervention (CIGITI) and SickKids interventional radiologist Dr. Michael Temple, Story Source: Focused Ultrasound Foundation on August 6, 2014.
[29] Yong Zhou, Wenxin Xing, Konstantin I. Maslov, Lynn A. Cornelius, Lihong V. Wang. **"**Handheld photoacoustic microscopy to detect melanoma depth in vivo**."** *Optics Letters*, 2014; 39 (16): 4731 DOI: 10.1364/OL.39.004731
[30] "Transcranial ultrasound therapy: New information gained from study" published in *Computerized Medical Imaging and Graphics*, *Physics in Medicine and Biology*, and *IEEE Transactions on Biomedical Engineering*. ***Story Source:*** University of Eastern Finland ***on*** August 4, 2014
[31] N. Huebsch, C. J. Kearney, X. Zhao, J. Kim, C. A. Cezar, Z. Suo, D. J. Mooney. "Ultrasound-triggered disruption and self-healing of reversibly cross-linked hydrogels for drug delivery and enhanced chemotherapy." *Proceedings of the National Academy of Sciences*, 2014; DOI: 10.1073/pnas.1405469111.
[32] Sanjay Agarwal, MD, director of Fertility Services in the Department of Reproductive Medicine at UC San Diego Health System and director of the UC San Diego Center for Endometriosis Research and Treatment (CERT). ***Story Source:*** University of California, San Diego Health Sciences on June 23, 2014.
[33] Bertrand Audoin, a professor in the mechanics laboratory at the University of Bordeaux, France, 57th

Annual Meeting of the Biophysical Society (BPS), held Feb. 2-6, 2013, in Philadelphia, Pa. Story ***Source:*** Biophysical Society ***on*** February 1, 2013.

[34] Dr. Paul Dayton, biomedical engineering department at NC State and Chapel Hill and Dr. Xiaoning Jiang, an NC State associate professor of mechanical and aerospace engineering, professor of biomedical engineering "A preliminary engineering design of intravascular dual-frequency transducers for contrast enhanced acoustic angiography and molecular imaging," is published in the May issue of *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*. Story ***Source:*** North Carolina State University on April 24, 2014.

[35] SAIJO, Yoshifumi , Professor (PhD (Medicine)), Biomedical Imaging Laboratory, Graduate School of Biomedical Engineering, http://www.ecei.tohoku.ac.jp/imaging/index-e.html

[36] Gail ter Haar, "Ultrasonic imaging: safety Considerations-REVIEW", Interface Focus (2011) 1, 686–697doi:10.1098/rsfs.2011.0029 Published online 25 May 2011, Downloaded from rsfs.royalsocietypublishing.org on November 9, 2014

[37] Bricker, L; Garcia, J; Henderson, J; Mugford, M; Neilson, J; Roberts, T; Martin, MA (2000). "Ultrasound screening in pregnancy: A systematic review of the clinical effectiveness, cost-effectiveness and women's views". *Health technology assessment* **4**(16): i–vi, 1–193. PMID 11070816.

[38] Kieler, Helle; Cnattingius, Sven; Haglund, Bengt; Palmgren, Juni; Axelsson, Ove (2001). "Sinistrality—a side-effect of prenatal sonography: A comparative study of young men". *Epidemiology* **12** (6): 618–23. doi:10.1097/00001648-200111000-00007.PMID 11679787

[39] Heikkilä, K.; Vuoksimaa, E.; Oksava, K.; Saari-Kemppainen, A.; Iivanainen, M. (2011). "Handedness in the Helsinki Ultrasound Trial". *Ultrasound in Obstetrics & Gynecology***37** (6): 638. doi:10.1002/uog.8962.

[40] Saranteas, Theodosios, Limitations in Ultrasound Imaging Techniques in Anesthesia: Obesity and Muscle Atrophy?, Anesthesia & Analgesia: September 2009 - Volume 109 - Issue 3 - pp 993-994, doi: 10.1213/ane.0b013e3181ae09a4

[41] Aaron Fenster, D´onal B Downey and H Neale Cardinal, TOPICAL REVIEW: Three-dimensional ultrasound imaging, Phys. Med. Biol. 46 (2001) R67–R99, www.iop.org/Journals/pb PII: S0031-9155(01)12089-0