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High frequency biomedical and industrial ultrasound applications

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Abstract: Technical advances and selected developments in high frequency (HF) (above 20 MHz) ultrasound are reviewed along with current clinical uses that include intraluminal, ophthalmic, dermatologic and odontologic imaging. Pre-clinical applications that entail research using small animal imaging are explored and molecular imaging that involves probes or biomarkers for illuminating specific targets and aiding in diagnosis is also examined. Application of micron resolution ultrasound images in bone structure analysis is pointed out and the motivation behind visualization of the living cells using super-high frequency sources operating close to 1GHz is discussed. A few selected applications of HF ultrasound imaging in non-destructive testing, particularly in detecting flaws in adhesion layers and bonding quality are also included. Future developments of HF ultrasound energy are pointed out.

Key words: Biomedical ultrasonics, diagnostic and therapeutic ultrasound, high frequency ultrasound imaging, high frequency ultrasound non-destructive testing

A. Introduction

This paper is primarily concerned with high frequency (HF) biomedical and industrial ultrasound applications. Main focus is on frequencies above 20 MHz, although, due to their uniqueness, also included are a few selected lower frequency applications that have recently made their mark in odontology and non-destructive testing. The increasing importance of HF echocardiography is emphasized, especially in intraluminal imaging, diagnosis of vasa vasorum and in monitoring of tumor angiogenesis by detecting flow in microvasculature. As the image quality is governed primarily by the transducers, first a brief review of the HF pulse-echo scanheads is given. Then, HF applications in ophtalmology and dermatology are discussed and an increasing interest in ultrasound equipment tailored to imaging of small animals is examined. Next, the potential of HF imaging in studies of ultrasound mediated drug and gene delivery and interaction of ultrasound and biological tissue is discussed. Basic research applications, such as the use of ultrasound biomicroscopy implemented at the frequencies above 100 MHz for examination of specific properties of the tissue and membranes and to study life cycles of cells are highlighted. The outcome of the sub-millimeter resolution ultrasound studies of bone structures is also summarized. Application of ultrasound as a tool for monitoring of cell structural changes evoked by extraneous stimulants such as chemo- or radiation therapy combined with contrast agents is pointed out and a potential fusion of ultrasound, optic and other imaging modalities is discussed. In industrial applications, non destructive testing is underscored, especially in quality control of welding, testing the uniformity of sub-millimeter thickness adhesion layers, quality of bonds and monitoring products in electronic industry. Finally, potential of high frequency imaging and its most likely development in the near future is discussed. To ensure information relating to the most current research, bibliography includes papers presented at a variety of scientific meetings or being in press at the time of this writing.

B. High frequency ultrasound imaging transducers

A majority of high frequency (>20MHz) imaging systems currently used in clinical and pre-clinical practice employs single element geometrically shaped transducers, similar to those described in [1]-[4]. Single element transducers suffer from limited depth of field, however, when mounted in mechanical scanners they are capable of producing a B-mode image with an axial and lateral resolution on the order of 40 and 80 microns, respectively [5]. Single element transducers were successfully employed in acquiring sub-millimeter resolution in eye [6] and skin images [7]-[8]. To improve image quality obtained with single element transducers annular arrays capable of enhancing depth of field were fabricated and tested at about 40 MHz [9]-[11].

However, the primary goal in HF transducer design is the availability of linear arrays, which would enable real time imaging and electronically controlled dynamic focusing. Manufacturing of HF linear arrays is relatively complex and only a few years ago the first attempts to build an array operating at the center frequency of about 30 MHz were reported [12]. Since then, development of a 35 MHz, 64 element, piezocomposite ultrasound array for medical imaging was described [13]. In general, frequencies above 30 MHz are of interest in imaging of small tissue parts in human and in small animal imaging [14] and the piezocomposite array's applicability for real time imaging of mice organs at the frame rates of up to 165 per second was confirmed. Complexity of the HF array fabrication can be somewhat relaxed by making use of 2-2 composites. This material features much lower lateral coupling coefficient than conventional solid PZT ceramics, and allows kerfless design and fabrication of

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single element electrodes using lithography. A practical implementation of 256 elements, 40 MHz linear array made of a flexible 2-2 piezoelectric composite material was recently presented at the IEEE Ultrasonics Symposium in Vancouver [15]. Also recently, a new approach for fabricating HF linear array, which employs laser micromachining, was reported [16]. The 70% fractional bandwidth prototype was designed to operate at 30 MHz. The kerf between 64 elements was 8 microns. 74 micron pitch corresponding to 1.5 wavelength offered an acceptable compromise between a large B-mode field of view and minimization of the undesirable grating lobes.

Overall, availability of HF frequency transducers enabled design of small animal scanners that operate at frequencies beyond 40MHz and allowed practical implementation of ultrasound biomicroscopy [17]-[19]. In addition to piezoelectric composites the most recent transducer technologies make use of single crystals such as PMN-PT [20] and thick-and thin piezoelectric materials. Thin film technique is gaining attention because it will allow integration of CMOS electronics tranceivers using 0.35 microns process technology and activation of the piezoelectric material with voltages compatible with CMOS technology. In contrast, thick film design makes use of screen printing technology [21]. This technology was used to design a 40 MHz, multi-layer, thick film transducer consisting of a passive PZT substrate, electrode and active PZT doped layer [21]. The 32 micrometers thick film exhibited over 40% coupling coefficient. To optimize lateral resolution during *in vivo* skin imaging a polymer-based lens molded on the front face and designed to yield f-number of approx. 2.5 was used.

This brief review of HF ultrasound imaging transducer technology would be incomplete without a succinct description of a promising new family of HF ultrasound transducers, which use non-piezoelectric transduction [22]. Transduction principle of these new devices is similar to that of a condenser microphone (that can also be used as an acoustic source) with a DC voltage pre-biased moving membrane. The devices are manufactured using integrated circuit technology. Because physical dimensions of an individual “condenser microphone cell” are on the order of 100 microns, the adjacent cells can be readily connected to form virtually any shape. This feature is of interest as it allows realization of an electronically swept annular array. As noted above, annular arrays offer desirable zoom along the acoustic axis and also can provide uniform image resolution independent on deflection angle. It is very likely that the “condenser microphone” cells, also termed capacitive micromachined ultrasound transducers or CMUTs, will result in significant improvement in image quality and that the pricing of CMUT arrays will be advantageous as they can be manufactured using proven solid-state technology. CMUT technology has already permitted implementation of relatively wideband transducers operating at any frequency between 5 and 15 MHz and efforts are underway to extend the operating range to well beyond 20 MHz. Potential applications of CMUT technology include 2nd harmonic imaging and intravascular ultrasound (IVUS) imaging devices, which require small array size and electronics microminiaturization. The implementation of 2D arrays for 3D imaging using silicon integrated circuits technology was detailed in [23]. The CMUT technology is particularly promising to enable 3D imaging and make the diagnostic examination operator independent.

From the above it can be concluded that the HF transducers and associated technology have made a significant progress and opened a new field of sub-millimeter resolution ultrasound applications. The immediate challenge is to fabricate linear array transducers for real time imaging covering the widest possible range of frequencies. In industrial applications to the best of the author’s knowledge, only single element transducers are used in the frequency range considered here.

Biomedical HF applications are reviewed in the next section and entail both those that are already implemented in clinical practice and those involved with pre-clinical research. Clinical applications include: ophthalmic, dermatologic, cardiologic and intravascular, and odontologic; pre-clinical ones involve primarily small animal imaging and the use of small animals as useful models in development of new therapies.

C. HF biomedical and clinical applications

High frequency, ultrasound imaging systems have been shown to be useful for imaging anatomical structures of the eye, small scale superficial structures typical of skin diseases, and noninvasive visualization of teeth [24]-[35].

Ophthalmic imaging: High frequency, ultrasound imaging systems are now being used for imaging of anatomical structures of the eye, including cornea, cilliary body, choroids and the anterior chamber of the eye, including retina [24].

The need for high resolution imaging in ophthalmic applications has been underscored by the increasing number of laser *in situ* keratomileusis (LASIK) surgeries. Evaluation (and possible correction) of the outcome of this procedure requires accurate (standard deviation on the order of one micron is desirable) anatomic evaluation of the changes induced in the cornea by LASIK. The thickness of the layers to be measured prior to and after corneal refractive surgery is on the order of several tens of microns. The results of such evaluations obtained using 50 MHz single element transducer and representing 3D thickness mapping of corneal layers scanning of corneal epithelium, flap and residual stromal thickness can be found in [25].

Even higher resolution than that needed for LASIK surgeries is desirable in a procedure of photorefractive keratectomy (PRK). In contrast to LASIK, where a tiny flap of cornea is removed to allow laser beam shaping of cornea, PRK does not involve any cornea incision and laser is applied directly to the surface of cornea to remove appropriate layer of cornea cells. PRK is considered to be an alternative for patients with relatively thin cornea, which prevents any cutting or incision. A

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few prototypes of HF ultrasound transducers, which provided axial and lateral resolutions of about 19 and 28 micrometers, respectively, have been developed [26]. The transducers can operate at frequencies in the vicinity of 80 MHz and initial testing indicated that they should be capable of distinguishing between epithelial and posterior corneal boundaries during corneal scan. Once the pulse-echo sensitivity of these transducers is optimized they also hold promise to be useful in monitoring of the blood flow in retinal vessels. Blood flow information increases diagnostic power during routine eye examination and is also desirable during ocular occlusion removal surgery. As the blood velocity in retinal vessels is on the order of 10 mm/s or less it is expected that the Doppler systems operating at the frequencies above 40 MHz would be needed to successfully detect and monitor the flow.

Dermatologic imaging Skin imagers operating at 20 MHz are already well accepted in clinical diagnostic practice, and can provide axial and lateral resolution on the order of 40 to 210 microns, respectively [27]. However, this frequency is inadequate for diagnosis of skin lesions in epidermis; visualization of epidermis is essential in assessment of the wound healing process. Successful imaging of dermis and epidermis was obtained by using 100 MHz imaging system described in [28]. The system is also applicable to diagnosis of skin tumors and differentiation between the benign and malignant tissue based on mechanical behavior of the human skin. In addition to diagnostic applications, imaging of skin is of interest to cosmetic industry as it allows monitoring the effects of cosmetics on (ageing) skin. The potential of real time 20 MHz elastography (see also section on elastography) in depicting the mechanical properties of human skin under suction stress *in vivo* was also reported [27], [29].

Odontologic imaging Odontology is defined as a study of structure or diseases of teeth and teeth vitality. Tooth vitality diagnosis using non-invasive ultrasound is of significant interest in dentistry. Such diagnosis is usually determined by intrusive stimuli, such as cool, heat or mechanical stimulation (poking) and is frequently leading to patient’s discomfort. The applicability of non-invasive ultrasound pulse-echo and pulse transmission techniques to determine status of dental tissue within the pulp cavity was proposed about four decades ago [30], [31] and is gaining attention as it minimizes patients discomfort. Pulp is largely composed of loose connective tissue, which includes blood vessels, nerves, fibroblast, odontoblasts, mesenchymal cells and ground substances [32]. An inflammation (caused by a developing cavity) leads to decreased blood flow into coronal and peripheral layers of the pulp, which eventually may result in necrosis of the tooth and bone with concurrent danger of introducing ancillary secondary infections and diseases, that may influence patient’s health. Ultrasound is capable of detecting flaws such as cavities, cracks and abscesses and a comprehensive set of experimental data obtained at 10 MHz was recently published [33]. The data presented in [33] included analysis of the A- and B-scans, performed on an intact tooth, a tooth containing an amalgam restoration and a natural surface fissure, a tooth containing a machine side-drilled hole that mimicked a cavity, and a calcified tooth. These results indicated that echodentography can be considered as a viable alternative to currently used x-ray based dental imaging systems. The possibility of employing ultrasound for dental tissue analysis was also evaluated *in vitro* using acoustic microscopes operating at 50 and 200 MHz [34]-[35]. Results of the evaluations indicated that several parameters, such as the thickness of enamel and dentine were readily determined along with the information on the distance from tooth’s surface to the pulp cavity. Acoustic microscope scan was also able to unveil deep-seated, invisible cavities and provided visual image of the dental restorative material. As noted above, such data are of importance to distinguish between the healthy- and diseased tooth pulp.

Cardiologic and Intraluminal Imaging Several clinical applications of HF ultrasound can be identified within the field of cardiovascular medicine. These applications are focused primarily on identification of vulnerable plaque-atherosclerotic lesions that are prone to rupture [36]-[38]. Vulnerable plaques are associated with inflammation and increased concentrations of pro-inflammatory markers. Clinically, either rotating 30-60 MHz single element transducer or 20 MHz 64 elements linear phased array catheters are being used to obtain intraluminal image of the blood vessels needed for diagnosis. Similar techniques are used in assessment of esophageal varices and measurement of wall thickness in esophagus and imaging of the urethra [39].

Three dimensional real time cross sectional images of blood vessels *in vivo* are used for detection and evaluation of coronary diseases prior to surgical intervention and for treatment monitoring. Detection and subsequent monitoring of angiogenesis and changes in *vasa vasorum* are also of immediate diagnostic and therapeutic interest. Angiogenesis may indicate development of malignancies, however it may also be intentionally induced by drugs or appropriate molecular therapies to stimulate blood vessel growth in ischemic tissues. Intentionally induced angiogenesis allows alternative blood circulation and may reduce the need for bypass surgery or angioplasty. The intentionally induced process of angiogenesis (e.g. during chemo- or radiation treatment of malignant tissue) is associated with structural changes at the cellular level. If quantifiable, such information could be utilized in monitoring of the anticancer treatment. As backscatter echo strength depends on the tissue structure and frequency it is likely that the analysis of the spectral slope, similar to the one proposed in [40] and applied for the eye and liver tissue characterization, could be used as an indicator of the treatment progress. Quantitative angiogenesis would permit the analysis of tissue microvascularization and hence would allow monitoring the progress of development of tumor cells. Development of biologically active contrast agents described in the following will further facilitate diagnosis of vulnerable plaque by identifying and monitoring the inflammatory markers.

Bone imaging Primary goal of studying bone tissue at the sub-millimeter or microns resolution is to obtain acoustic and structural information that could be useful in determining bone architecture and its viscoelastic

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properties [41]. Experiments carried out with 200 MHz time-resolved scanning acoustic microscopy (TRSAM) showed that acoustic impedance could be used as an indicator when detecting genetic variations of the skeletal phenotype in small animal models. The TRSAM system allowed bone architecture and tissue elasticity to be determined with 8 microns resolution. However, limited penetration depth confines acoustic microscopy applications to *in vitro* tissue samples or cell imaging.

Small animal imaging – pre-clinical applications Small animal imaging is recognized as an important tool in enhancing diagnostic power of ultrasound and testing new imaging approaches, such as contrast agents and elastography [17]-[19]. Small animals - usually mice or rats - constitute excellent models for a variety of (pre-clinical) studies such as disease and genomic research, developmental biology and drug development [42]. They are also important in studying response of tumors to applied therapeutic treatment and obtaining a better insight of tumor angiogenesis [43]. Such pre-clinical uses are needed to develop clinically applicable diagnosis and treatments. Major research effort is directed towards embryo development, however, as noted earlier, this area of research would greatly benefit from the availability of linear arrays. This is because it is desirable to perform developmental and functional studies in real time. The additional challenge is due to the fact that these small animals exhibit heartbeat at a rate higher than 300 per minute, so implementation of real time imaging requires a frame rate on the order of 100 per second [13]. Feasibility studies aiming at the development of reliable methods of tissue characterization are also carried out using small animal models [44]. Initial experiments with a mammary carcinoma induced in mice indicated that power spectrum analysis (originally suggested in [40]) in the frequency range 30-90 MHz could be used as a classifier distinguishing healthy and malignant tissue and allowed scatterers' size (approximately 14 microns) to be related to the tumors [44].

Contrast agents at high frequencies Availability of small animal models and HF imaging systems has also prompted rapid advancements in the field of ultrasound contrast agents (CA) [45], [46]. Possibilities of using CAs in image enhancement as targeted drug delivery vehicles and in functional ultrasound studies are also actively examined using small animal models. Such research activities are needed because properties of contrast agents at high frequencies may differ from those developed for lower MHz frequencies. Physical dimensions of microbubbles at the HF frequencies are smaller and that will most likely influence their dynamics. Small, submicron diameter bubbles tend to vibrate isothermally, whereas vibration amplitude of the larger bubbles is governed by the adiabatic value of the polytropic exponent [47]. To survive in blood environment the tiny bubbles have to be encapsulated with biocompatible surfactants or polymers [48], but once the bubbles are produced they do not need to be air filled – at the expense of the reflectivity they can be partially filled with medicine or drugs. In addition, bio-coating offers an opportunity for targeted drug delivery.

Elastography imaging, which has been developed in recent years [49]-[53], holds promise of enhancing diagnostic power of ultrasound, especially in detecting tumors in soft tissue and differentiating malignant and benign tumors. Also, it may be useful in characterization of vulnerable plague [54]. In addition, in the recent studies performed using small animals, myocardial elastography was determined to be a promising method in noninvasive evaluation of regional myocardial function. Elastography images of murine infarcts were obtained at 30 MHz using mechanical sector scanner [55]. The same 30 MHz scanner was used in studies examining the possibility of aneurism detection in murine abdomen [56]. Early detection of the abdominal aortic aneurysm is crucial because of its inclination to rupture with the associated complications. It was demonstrated that pulse wave imaging used for mapping of the propagation along the wall of the abdominal aorta in a murine model was able to determine aorta's elasticity from the strain and the velocity of the wave in the aorta using the gradient and phase shift estimation techniques. The study [56] has shown that the measurement of aortic wall stiffness could be used as an early warning indicator of the possible aneurism rupture.

D. Emerging high frequency technologies

Coded excitation: As mentioned earlier, due to the overall attenuation [9] the visualization of the bottom of the eye to diagnose retinal disease such as macular degeneration or detached retina at the desirable, 40 MHz or higher frequencies is difficult. However, the penetration depth could be improved by applying coded transmission [57]-[61]. Advantage of the coded transmission techniques is their ability to improve quality of the image by enhancing signal-to-noise ratio (SNR) without the need to increase the peak pressure amplitudes of the probing waves. Of the coded transmission schemes proposed, one of the most promising at HF is complementary Golay code as it leads to elimination of side lobes [61].

Harmonic Imaging Another approach to overcome attenuation is to design a HF pulse-echo system that is capable of second harmonic imaging. Such system would launch the probing wave at the fundamental frequency of 20 MHz and receive the echoes at 40 MHz. A prototype of an HF system operating at 2nd harmonic has been recently tested using a conventional continuously rotating catheter [54]. Comparison of the images of the cross-sections of rabbit atherosclerotic aorta obtained at 20 and 40 MHz confirmed that the higher frequency (i.e. 40 MHz) image provided better image quality. Harmonic imaging at HF is also expected to be useful in detection of flow in the *vasa vasorum* using HF contrast agents [48].

Studies and imaging of cells Studies of unharmed living cells using ultrasound are of significance in understanding their reaction to external stimulants such as drugs and ionizing radiation. These two stimulants, which are the key ingredients in chemo- and radiation cancer therapy, may trigger a variety of physiological events, including apoptosis and proliferation. Time Resolved Acoustic Microscopy (TRAM) [62] is often preferred in studying living cells dynamics because it

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provides high resolution characterization of the cell volume and, in contrast to laser light microscopy, does not introduce artifacts due to "light bleaching" effect and leaves the cell's functionality undisturbed. The B mode images obtained using TRAM at 1 GHz to monitor living L-929 fibroblast cells [62] indicated that a pixel distance of 0.8 microns was achievable. Although lateral resolution of acoustic microscopy at 1 GHz is somewhat lower than that of light laser microscopy, the axial resolution is considerably higher and studies were performed to determine the possibility of combining acoustic and optic microscopy. Such combined system comprising 1.2 GHz acoustic- and fluorescent optic microscope was proved to be useful as a tool for functional imaging of living cells when employed in the study of adhesion properties of the chicken heart muscle cells [63]. TRAM imaging is well suited to study cell dynamics, however, the mechanical properties of cells can be more readily determined using phase sensitive acoustic microscopy system. Combined 1.2 GHz phase-sensitive acoustic microscopy (PSAM) and confocal laser scanning microscopy (CLSM) in reflection and fluorescence, respectively, was recently proposed [64]. The PSAM-CLSM system allowed collection of acoustic (amplitude and phase) and optical images of the same area of the sample concurrently. Cells parts were easily distinguishable in the presented 10x100 microns surface images. In addition to examining cells' response to external stimuli, study of migration and adhesion of cells is of importance in many cellular activities such as embryo development, wound healing and malignant cell development.

Molecular Imaging Growing research in ultrasound molecular imaging involves probes or biomarkers that could identify or illuminate specific targets. Illumination of these specific targets, such as malignant cells usually entails increasing their echogeneity or requires attachment of optically detectable fluorescent markers. The enhancement of acoustic reflectivity or optical visualization helps in diagnosis or monitoring of the cells response to a drug or radiation treatment using ultrasound biomicroscopy [14]. Such approach aided in labeling dead and apoptotic cells [65]. Hence, advances in the development of innovative therapies at the cellular level are dependent on the ability of imaging the effects of a given stimulant, be it drug or radiation treatment on a molecular level [65]. Overall molecular imaging holds promise to enhance diagnostic power of ultrasound examination. Ultrasound biomicroscopy can be used to image angiogenesis and identify apoptosis, which is an important indicator of the cell response to the therapy [65]. Microbubbles can be used as targeted ultrasound contrast agents and facilitate detection of tumors and inflammation sites. Specially prepared microbubbles can also be used as vehicles for therapy and targeted drug delivery; they can also amplify the effects of ultrasound mediated gene transfection. A broad overview discussing potential of ultrasound in molecular imaging can be found in [14].

Industrial Applications In industrial applications, non-destructive testing is indispensable especially in quality control of welding, testing the uniformity of sub-millimeter thickness adhesion layers, and determining the quality of bonds [66]. In electronic industry it is essential in monitoring detection of flaws in semiconductor wafers and in testing of the new dense metal lines memory chips using 60 nm (and soon 33 nm) wide resistive connections with a similar size of spaces between the adjacent lines. In automotive industry the need for HF imaging systems was generated by introduction of composite materials, which, to a large extend, replaced metal body parts. This development reduced susceptibility to corrosion, lowered vehicle weight and hence improved fuel efficiency and last but not least, increased robustness of the construction. Introduction of composite materials generated a need for a reliable testing of adhesive bonds quality [66]. Such testing is presently performed using commercially available 1—20 MHz pulse-echo systems. Evaluation of the uniformity of sub-millimeter thickness adhesion layers requires the use of higher frequencies. It is well known that the adhesion strength depends critically on the curing process [66]. Cohesive acoustic and physical and chemical properties of the bond can be monitored by measuring attenuation and sound velocity whereas quality of the cured bond microstructure can be examined by performing scanning acoustic microscope and producing C-scan image of the bonding boundary. Side by side 250 MHz C-scans taken at 0, 10 and 35 minutes after elapsed curing can be found in [66]. In addition to C-scan, B-scan images that can reveal size and depth position of the flaws or delamination (e.g. in the multilayer PC boards) are used.

E. Ultrasound metrology beyond 20 MHz

The review presented above indicates a growing need for quantitative measurements of ultrasonic fields in the frequency range that exceeds 20 MHz. As noted earlier, clinically used frequencies are currently approaching 80 MHz in eye scanning applications [26]. Quantitative measurements of ultrasonic fields require availability of calibrated hydrophone probes. However, presently available piezoelectric probes are not fully adequate for this purpose due to their finite aperture, which introduces spatial averaging error and also because the probes' frequency response is usually insufficient to cover wide, 100 MHz bandwidth [67]-[69]. To eliminate the need for spatial averaging correction at 100 MHz effective diameter of the probe should be on the order of 7 microns; such probes are currently under development [69]. Availability of hydrophone probes using fiber optic will provide an alternative to the currently used PVDF polymer probes, if the small physical dimensions and the elimination of the spatial averaging error are of immediate concern in the field measurements. However, the PVDF probes are in general easier to operate and an appropriate signal processing can provide the spatial averaging correction.

F. Conclusions

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

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ultrasound in dermatology, odontology and ophthalmology are also rapidly increasing. Ultrasound transducers operating at frequency of about 50 MHz are successfully used in investigating physiology of small animals. These animals are considered to be excellent candidates for models in studies of ultrasound mediated drug and gene delivery and interaction of ultrasound and biological tissue. Moreover, 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. Sub-millimeter 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 holds promise of further enhancement of diagnostic power of ultrasound, especially in detecting tumors in soft tissue, differentiating malignant and benign tumors, and in detection and characterization of vulnerable plaque. Elastography images will aid in diagnosis by providing an alternative and complementary image to that obtained using B-scan but an informed use of this new technique will require understanding of the mechanical behavior of the tissues. 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 conceivable that ultrasound scans could be combined with the functional information obtained from microPET scanner to optimize cancer detection and monitor the progress of therapy. 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.

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H. Literature

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