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Current and Emerging Ophthalmic Diagnostic Imaging: A Review

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Abstract

A review of current and emerging ophthalmic diagnostic imaging techniques has been presented. Fundamental physical principles behind the imaging techniques are discussed along with their application areas and limitations. The potential for high resolution 3D ophthalmic anatomical and functional diagnostic imaging using ultra- wideband (UWB) radar techniques for more accurate diagnosis and monitoring of ophthalmic medical conditions has been explored. Finally, a Micro-Electro-Mechanical Systems (MEMS) based novel UWB radar for non-contact noninvasive non-ionizing 3D real-time diagnostic imaging of eyes has been presented.

Keywords: *Ultra-Wideband (UWB); Micro-Electro-Mechanical Systems (MEMS); Ophthalmic Diagnostic Imaging Techniques*

Introduction

Ophthalmic diagnostic imaging involves probing the eye with an energy source to collect data that can be analyzed using 2D or 3D graphical means to detect any anatomical or functional medical condition. Both ionizing radiation, such as X-ray, and non-ionizing, such as electromagnetic radiation or ultrasound, are used [1]. Sometimes, radioactive substances (tracers) and contrast agents are used to improve the quality of data to aid better diagnosis. Some of these techniques are invasive and some needs the electrodes or the probes to be in contact with the patient's body. The imaging resolution and accuracy also vary from technique to technique.

The information that is collected by difference techniques is not essentially the same and are typically useful for diagnosis of different anatomical and functional medical conditions. For example, the X-ray method uses external ionizing radiation to visualize the anatomical structure, but single photon emission computed tomography (SPECT) method collects the functional image of an organ using clinically administered radioactive tracers. X-ray imaging can provide information about the physical anatomical structures but cannot provide dynamic imaging such as muscle contract, stiffness of tissues, blood flow or pressure. In [2], it has been mentioned that "though computed tomography (CT) presents a better spatial resolution as compared to positron emission tomography (PET), CT is less informative in soft-tissue functional imaging than PET." As the imaging resolution depends on the wavelength, the resolution of low frequency ultrasound images is poorly compared with magnetic resonance imaging (MRI) or computed tomography (CT) image resolutions. Furthermore, being an ionizing radiation, X-ray increases the risk of cancer. The accuracy of ultrasound imaging depends on several factors including operator expertise. Some of this diagnostic imaging equipment are expensive, depending on the type of technology, for example MRI, PET, or SPECT can be available only at hospitals or large specialized clinics.

The imaging transducers also play a crucial role in the quality of imaging data. The capability of a transducer in resolving minimum features in terms of spatial (both vertical and horizontal), axial (anteroposterior), contrast, and temporal resolution affects the image quality. Interpolation, apodization, or other digital image-enhancing techniques are used by the imaging practitioners to improve imaging quality with varying degrees of success. The situation is more challenging for the eye due to its subtle physiological importance and complex anatomy.

A review of the existing diagnostics imaging technologies presented in [3] summarized that "there is, at present, no technique for the imaging of internal structures of the human body, which applies universally to all tissues, has high resolution, is inexpensive, uses non-ionizing radiation, creates images in real-time, and can be conducted in the office of a dentist office" [3]. The remarks made in [3] apply equally to the anatomical and functional imaging of the eye as well.

In this context, this paper reviews notable existing ophthalmic imaging techniques. Advances in medical imaging techniques for other areas including multi-modal approaches are also discussed. Finally, an emerging micro-electro-mechanical systems (MEMS) microwave sensor array based ultra-wideband (UWB) radar technique has been presented.

Existing common diagnostic imaging technologies

Ultrasound

Low and high frequency ultrasound remains one of the key investigative tools for anatomical and functional diagnostic imaging of human internal organs, including the eye. Low frequency ultrasound in the range of 2-10 MHz is used for common diagnostic imaging of organs deep inside the body, such as the heart, abdomen. High frequency ultrasound is also being researched to acquire higher resolution images as the higher the imaging frequency, the finer features can be resolved to improve diagnosis accuracy [4]. In [5] it has been mentioned that "The Vevo™ family of high frequency ultrasound products enables the researcher to obtain *in vivo* anatomical, functional, physiological and molecular data simultaneously, in real-time with a resolution down to 30 μm [5]". Use of 2D arrays enables one to acquire 2D image slices that can be stacked to form 3D image. Ultimately, the imaging industry will move to 3D, or more precisely real-time 3D where a radiologist can rotate the image and slice it to see the internal tissue structures as a function of time [6].

With the advancement of the manufacturing methods of piezoelectric materials and the development of capacitive micromachined ultrasonic transducers (CMUTs), high frequency static and color Doppler 3D ultrasound can become an excellent candidate for anatomical and functional diagnostic imaging of eyes and can compete with CT and MRI for some imaging applications [7]. In [8] it has been mentioned that "Color Doppler ultrasound has successfully demonstrated changes in orbital hemodynamics associated with various pathological conditions, including central retinal artery and vein occlusions, cranial arteritis, non-arteritic ischemic optic neuropathy, and carotid disease." However, one of the main drawbacks of 2D or 3D ophthalmic ultrasound is that the transducer (array) needs to be in physical contact with the eye, the acquired signal is pressure dependent, and accuracy depends on the skill of the operator [9]. Any error in transducer placement and statistical and signal processing challenges degrade the quality of the image to compromise diagnostic accuracy further.

Computed tomography

Computed tomography (CT) scanners are available to detect tumors and cancer spread inside an eye and the neighboring areas [10]. Such scanners use special X-ray radiation and in some cases contrast agents to create 3D and cross-sectional images of the eye. Some high resolution CT scanners can acquire and reconstruct images with sub-millimeter resolution slices [11]. Different variations of CT, such as "CT angiography (CTA), CT venography (CTV) and dynamic perfusion CT (PCT)" used in neuro- ophthalmic and orbital imaging have been reported [12]. However, harmful X-ray ionizing radiations and contrast materials that are used for various CT modes put some limits on the doses and number of exposures to safeguard against any harmful radiation-related complications, especially for child patients [12].

Magnetic resonance imaging (MRI)

MRI is becoming an attractive ophthalmic imaging mode due to its high resolution, non-contact non-ionizing imaging qualities and as this mode can be used to image both anatomical and functional imaging [12-14]. The authors in [14] mentioned that "*In vivo* magnetic resonance imaging (MRI) of the optic nerve and the extraocular muscles can provide substantial benefits in understanding oculomotor functioning in health and disease." Different variations of MRI are available for ophthalmic imaging [12,13]. MR angiography (MRA) is used to evaluate blood flow in the eye vascular system. Sometimes to enhance the imaging quality, a contrast agent is used. Another MRI technique known as magnetic resonance venography (MRV) uses an intravenous contrast agent to make the blood vessels opaque to image them. Fluid attenuated inversion recovery (FLAIR) technique is used to suppress the fluid reflected signal during MRI to improve the visualization of any lesion near the fluids in eye blood vessels [15]. Gradient recall echo imaging (GRE) is another new technique of MRI that can detect the smallest changes in uniformity in the magnetic field and can improve the rate of small lesion detection changes in tissue biochemical components that may help early quantitative detection of a disease [16]. Diffusion-weighted imaging (DWI) is another advanced MRI technique that uses the diffusion properties of water molecules due to Brownian motion that can be used to differentiate malignancies at an early stage [17]. Perfusion-weighted imaging (PWI) is another emerging MRI technique that uses monitoring of a non-diffusible contrast material to the eye tissues to determine the presence of any lesions or blood flow obstruction [18].

Functional MRI (fMRI) can be used for noninvasive imaging of neural functions without the use of any contrast agent with a relatively high resolution [19]. The efficacy of fMRI can be further enhanced if it is possible to use the more powerful MRI machine such as INUMAC MRI, that is a "11.75 T MRI machine that can image an area of approximately 0.1 mm or 1000 neurons and help us see changes occur as fast as one- tenth of a second, which is far superior to the standard MRI resolution of 1 mm at 1 second" [20].

Thus, different variants of MRI can acquire static and dynamic structural and behavioral data of eye tissues, blood vessels and nerves that can be used to diagnose medical conditions with high accuracy at an early stage by providing information about any tiny pathological change in the cell structure. Moreover, all of these can be achieved non-invasively without using any harmful radiation.

PET and SPECT

Both PET and SPECT use externally induced radioactive materials and image their concentration at the cellular and sub-cellular locations to diagnose any medical condition. In SPECT, many images collected using Gamma camera detectors from different angles are used to generate computed 3D images of the gamma ray emissions from radioactive tracers accumulated in the target area [21]. In PET, different types of radiotracers (isotopes) are used that decay to generate positrons, which combine with electrons in the target area to emit photons. A scanner collects these photons from different angles to generate a 3D image. PET provides a decisive tool to diagnose orbital and ocular cancer, differentiate between benign and malignant tumors and monitor the progress of a treatment [22].

The main disadvantage of PET and SPECT is that they are highly expensive, not readily available at all locations, though they can accurately identify the tissue functional behavior or response with a high resolution. In addition to detecting cancer, they can be used for examining the vascular system to identify any clogged or narrowed down blood vessels. In [12], it has been mentioned that "PET has superior sensitivity and tissue resolution and is the preferred study compared with SPECT." Prospects and limitations of PET and SPECT for ophthalmic imaging application are discussed in detail in [12]. However, the introduction of radiotracers in eyes to inspect blood vessels or orbital lesions possess a risk, though the techniques seem safer to image other areas.

Tissue electrical property imaging

Electrical impedance/conductance imaging

In a side by side development, there has been significant progress in using electrical properties such as conductance, resistance, and dielectric constant of tissues, bones, and fluids to create 2D and 3D images. Both static 2D images and 3D computed tomographic techniques are available. Based on the available literature, ophthalmic imaging using electrical properties of eye tissues is a less explored area. A technique called "Magnetic Resonance Electrical Impedance Tomography (MREIT)" is worth mentioning here [23-28]. The technique is noninvasive but needs contact pads for electrodes. During imaging, a current density is induced sequentially inside the body with 2 external electrodes and the impedance is measured at different locations using a set of additional electrodes and the voltage is measured. A typical MRI equipment is used at the same time to induce magnetic resonance and measures the current injection induced magnetic resonance phase shifts. An algorithm is then used to generate an impedance map. The selected tiny volumes over which the impedance is measured to create the impedance map determine the resolution. The technique is repeated rapidly to reconstruct a cross-sectional image. A computer simulation based study in [29] reported that "spatial resolution of resistivity image in MREIT is comparable to that of MRI." However, the requirements to set up current injection electrodes in an MRI set up limits its application and the availability of small electrodes that can be attached around the eye to obtain sufficient resolution pose a big obstacle for using this technique for ophthalmic imaging.

Another interesting tomographic method known as the "Magnetoacoustic Tomography with Magnetic Induction (MAT-MI)" senses the ultrasonic vibration generated in the tissues due to an induced Lorentz force [30]. During the process, the target tissues are simultaneously exposed to a static magnetic field and to a time- varying magnetic field. The time-varying magnetic field generates an Eddy current that with the perpendicular static magnetic field creates the Lorentz force, which is perpendicular to both the static magnetic field and the electric field to create an ultrasonic vibration of the tissues [30]. The frequency of the ultrasonic vibration depends on the frequency of the time-varying magnetic field and the vibration amplitude depends on the magnitude of the Eddy current. The reflected ultrasound wave can then be detected using a typical ultrasound probe to generate an ultrasonic spatial image that can be calibrated as a function of the local conductivity of the tissues. The technique is promising; however, while the magnetic field generation is noninvasive, an ultrasound probe needs to be in contact with the eye unless some method is invented for non- contact ultrasound imaging. The author in [30] claimed that "they could generate images with mm to sub-mm scale resolution and MAT-MI method can become a clinically applicable, high resolution, noninvasive method for electrical conductivity imaging." However, in addition to being a bit cumbersome, and expensive due to the requirement of powerful magnets (typically from an MRI machine) and possible inconvenience with the placement of the ultrasound probe, the resolution is not suitable for ophthalmic imaging requirements.

A new technique called "Magnetic Resonance Electrical Properties Tomography (MREPT)" was used in an *in vivo* experiment using a 3 T MRI system to image the electrical properties (permittivity and conductivity) within a human head and leg [31]. An improvement of the MREPT technique using a 9.4 Tesla MRI machine is reported recently that is less prone to RF noise [32]. However, any ophthalmic use of the technique is yet to be reported.

Tissue dielectric property imaging

A microwave imaging technique exploits the variation of complex permittivity from point to point in an inhomogeneous subsurface such as tissues to generate a map of regions of different permittivity (2D microwave tomography). Alternatively, the system can generate an image of the regions with the highest concentration of scattered energy [33]. The fundamental physics behind this medical diagnostic imaging technique relies on the fact that microwave scattering and absorption characteristics of tissues inside the human body depends on the complex permittivity of human tissues, which are influenced by physiological factors such as water content, sodium content, temperature, and vascularization [33,34]. As the technique is non-contact and uses non-ionizing radiation, can become a suitable mode of ophthalmic imaging to detect cancer or other pathological changes in ocular tissues.

Ultra-wideband (UWB) imaging

Another emerging development in diagnostic imaging that has great potential for non-contact noninvasive non-ionizing imaging of eyes is the ultra-wideband (UWB) radar technique. A UWB radar transmits a sequence of short-duration pulses of picoseconds to nanoseconds duration over a large bandwidth to result in a lower power spectral density over a UWB spectrum. The typical bandwidth of a

UWB signal is approximately 1.5 GHz or more and the designated UWB spectrum is 3.1 GHz - 10.6 GHz [35]. Different frequency components of such a short-duration non-sinusoidal UWB pulse attenuate at different rates as they interact with soft and hard tissues during propagation. This interaction affects the waveform and the power spectral density (PSD) of a pulse reflected from a tissue boundary characterized by a permittivity change. The amount of change depends on the depth and the frequency dependent complex permittivity of the interacting tissue layer. Thus, by comparing and analyzing the reflected UWB waveform, magnitude, and power spectral density, it is possible to extract the permittivity of the interacting medium or tissue boundaries. As the diseased or healthy soft or hard tissues are characterized by different permitivities, it is possible to create a permittivity map that can show the permittivity distribution as a function of spatial variation [36-41].

As some of the incident UWB signal gets transmitted through a tissue layer, it gets reflected from a next dielectric boundary like the ultrasound waves and will arrive at the receiver later. Thus, a clock pulse of suitable duty cycle can be used to read the successive receiver value and map them in a 2D space. The shorter the clock pulse duration, the shorter axial resolution can be resolved. No change of permittivity (the same tissue or cell) will provide the same received value, whereas any change in permittivity will result in a different value in the map. A 2D array of UWB sensors of suitable size can be used to generate 2D images and 3D stacks of such images can generate a 3D image similar to a 3D computed topographic image. Following [3], a "matrix filter" realized using microwave absorbers can also be used along with a UWB receiver to realize a 2D power map of a reflecting permittivity boundary.

One advantage of this radar technique over the computed tomography method is that it is also possible to record the time response of a spatial location of a dielectric boundary to obtain a dynamic response that can provide additional information about the tissue layer, for example, stiffness, velocity, or displacement. As the stiffnesses of healthy and diseased tissues are different, high resolution maps of tissue permittivity and stiffness can provide accurate information about the tissue properties.

Though relatively new, experimental UWB radar based tissue static and dynamic response-based evaluation and monitoring of patient medical conditions including internal hemorrhage is available [38]. Experimental evidence presented in [39] shows that "microwave returns from several superimposed yet distinct layers of different dielectric materials when transformed into the time domain indicate the exact depth at which the layer changes and propagation characteristics distinct to each layer traversed." That verifies the efficacy of a UWB radar in evaluating medical conditions that involve both anatomical and functional changes to diagnose any malignancy, benignity, or internal hemorrhage.

This proven capability of UWB imaging technology can be extended to the area of ophthalmic diagnostic imaging. The major advantage of the UWB radar based ophthalmic imaging lies in the fact that the UWB imaging can be done in a non-contact, noninvasive manner without any ionizing radiation or contrast agent and both functional and anatomical information can be performed irrespective of age, including infants. As the target imaging depth is relatively short, the UWB signal loss will be smaller and relatively lower power spectral density can be used. Objects with low contrast in acoustic impedance, X-ray CT, or electrical impedance tomography, can be of higher contrast from the permittivity perspective and can be imaged with high resolution, especially any early stage tumor or lesion in the eye., The authors in [40] opined that "depending on requirements, the UWB technique can operate in radar mode, in tomography mode, or a novel unique combination of both" to generate dynamic high resolution 3D functional or anatomical images. Such non-contact noninvasive 3D imaging can be used during laser eye surgeries as well to improve accuracy.

In [38] it has been mentioned that "UWB radars and ultrasound are very similar and many of the signal processing techniques used in ultrasonic systems can be applied to UWB systems". As the power spectral density of the UWB pulse is low, it will be easier to follow and implement the standards and guidelines provided by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) exposure limit to set an UWB power limit that is not harmful to the eye [42].

MEMS technology

The advantages of the UWB technology can be further extended by exploiting the capabilities of the emerging Micro-electro-mechanical Systems (MEMS) based miniaturized high performance sensor technology.

MEMS technology exploits microscale physical phenomena to design superior performance microscale transducers and actuators that can be microfabricated using processes that are in use to manufacture conventional microelectronic integrated circuits (ICs). However, unlike the solid state microelectronic integrated circuits that do not have any moving parts, the MEMS devices incorporate micro and nanoscale beams, thin diaphragms, and other types of vibrating and resonating microstructures with innovative geometries to enable sensing and actuation with high precision, quality factor, and sensitivity that are not possible with conventional macroscale technologies [43]. As the manufacturing process is similar, the controlling microelectronic integrated circuits can be fabricated or integrated easily with MEMS devices to achieve higher performance, reliability, minimized interconnection losses to improve the signal-to-noise ratio (SNR), and data quality. The resulting systems can be applied for energy transduction and information processing in any energy domains such as acoustics, electromagnetics, fluidics, photonics, and quantum mechanics with applications in the areas of biomedical, automotive, environmental protection, avionics, entertainment, and industrial manufacturing [43].

As the MEMS-based sensors are very small, of the order of millimeter or sub- millimeter range, and can easily be realized and integrated with control electronics, the complete system can be made very small and manufactured at a lower cost to be affordable at the office of ophthalmologists. Accordingly, there is a great potential that MEMS-based UWB 3D imaging radars can provide small eye clinics and ophthalmologists with imaging and diagnostic capabilities currently available only in hospitals.

MEMS microwave sensor based ophthalmic UWB radar tomography

Based on the review of the state-of-the-art imaging technologies and their relative advantages for various ophthalmic diagnostic imaging applications, it appears that non- contact noninvasive and non-ionizing modes capable of generating high resolution high contrast 2D and 3D structural and functional images of target eye tissues are preferably compared to other modes. Some imaging modes, such as MAT-MI, MREIT, PET, or SPECT, despite their relatively high resolution imaging capabilities, most likely, not going to have widescale ophthalmic diagnostic imaging applications due to expensive equipment and related maintenance costs. High frequency ultrasound is a promising approach but due to the fact that the fabrication of piezoelectric high frequency ultrasound transducers is difficult and the requirement of contact mode operation with the skin, appears not to be an attractive option for ophthalmic diagnostic imaging. Various MRI modes are highly accurate and non-contact but expensive. This limits their availability only in hospitals or specialized clinics.

In this context, a new MEMS microwave sensor based UWB radar for ophthalmic diagnostic imaging application is proposed. The non-contact, noninvasive, and non-ionizing technique is capable of generating 3D images that can be viewed also as 2D thin slices. Due to superior MEMS technology, the device can be fabricated at a low cost using the conventional microfabrication technique using standard process sets in a small form factor. A block diagram of the MEMS microwave sensor based UWB radar is shown in figure 1.

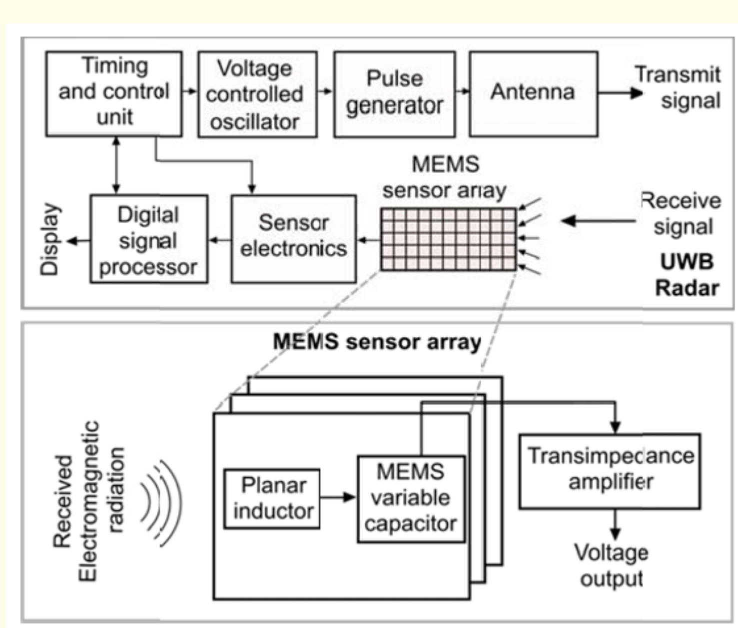

Figure 1: *Block diagram of UWB radar with MEMS sensor array.*

The proposed radar comprises an UWB transmitter module and a MEMS microwave sensor module. The UWB transmitter module generates and transmits a short-duration non-sinusoidal pulse train within the UWB frequency range using a high precision voltage controlled oscillator (VCO), a pulse generator, and an UWB antenna. The MEMS microwave sensor module is a 2D array of a MEMS microwave sensor that is the core innovative technology of the system. The MEMS microwave sensor is designed to have a planar inductor and a MEMS vibrating diaphragm variable capacitor [43].

During the operation, the UWB radar transmitter transmits a short-duration UWB pulse train with a desired pulse repetition frequency. As the UWB pulse train illuminates the eye, it penetrates through the eye tissues and starts to attenuate during propagation through the tissues and reflects back from a tissue boundary characterized by a permittivity change. The degree of attenuation and reflection coefficient depends on the frequency dependent complex permittivity of the interacting tissue segment and the respective dielectric boundary. As the reflected UWB pulse is incident on the MEMS microwave sensor, the inductor acts as a loop antenna to generate a voltage across its terminals following Faraday's law of electromagnetic induction. This voltage appears across the MEMS capacitor to generate an electrostatic attraction force between the diaphragm and backplate to cause a deflection of the diaphragm. This deflection changes the capacitance between the capacitor electrodes (diaphragm and backplate) which is converted to an output voltage using a transimpedance amplifier. As the resonant frequency of the diaphragm is designed to be much smaller than the operating UWB frequency band, the diaphragm deflection depends only on the rms value of the generated electrostatic force. Figure 2 shows a linear array of the sensors generating output voltages corresponding to an incident electromagnetic wavefront at different time intervals. A 2D array of such sensors can generate a 2D voltage map corresponding to a 2D spatial distribution of a wavefront as shown in figure 3. The 2D values from different depths can be read at different time intervals and processed to generate a 3D image of the target area as shown conceptually in figure 3. The registered values can be stored in memory, calibrated, and presented in 2D or 3D graphical format to identify functional or anatomical features of the eye.

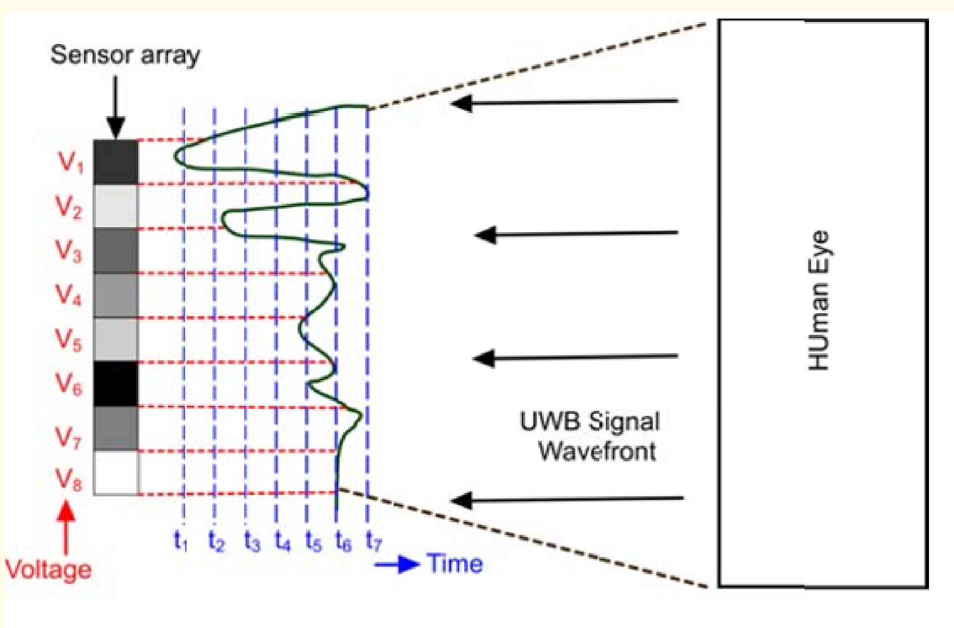

Figure 2: *Signal received at different time intervals from different permittivity boundaries.*

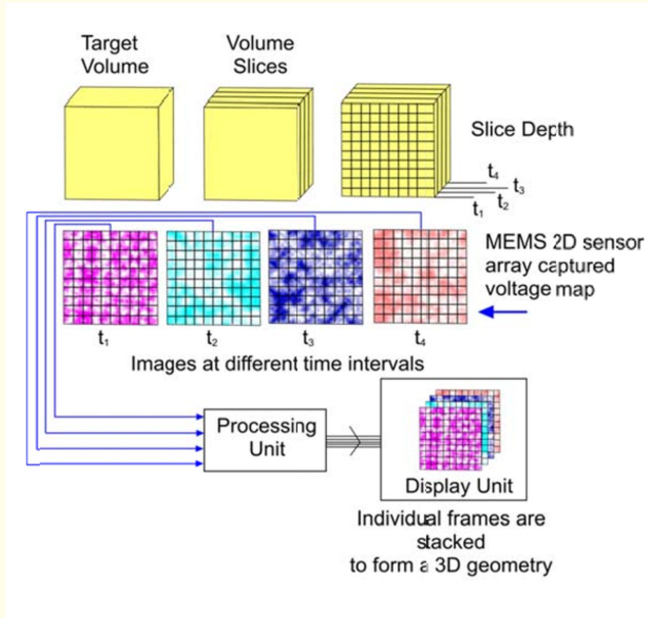

Figure 3: *3D tomographic image generation using the MEMS-based sensor array.*

A finite-difference time-domain (FDTD) analysis of an UWB radar based MEMS sensor array shows that such a system can generate an output voltage from a depth of 42 mm inside a human body [43]. The sensor presented in [43] has a footprint area of 595 x 595 μm^2 and exhibits a linear capacitance change - induced voltage relation and a calculated sensitivity of 4.5 aF/0.8 μA/m.

The CT scan measurements of transverse (horizontal), sagittal (vertical) and anteroposterior (axial) dimensions of a human eye reported in [44] are listed in table 1.

Parameter	Value	Unit
Transverse (horizontal, orbit width)	24.2 (Range: 21 - 27)	mm
Sagittal (vertical)	23.7	mm
Anteroposterior (axial)	22.0 - 24.8 (Range: 20 - 26 in cases of myopia and hypermetropia)	mm

Table 1: *CT scan measured eye dimensions [44].*

As the measured dimensions of the eye as shown in table 1 are much smaller than 42 mm, there is a high possibility of realizing a UWB radar with a MEMS sensor array for ophthalmic 3D imaging with high transverse (horizontal), sagittal (vertical) and anteroposterior (axial) resolution. The methodology presented in [43] can be followed to design the proposed MEMS microwave sensor based UWB radar.

Conclusion

A review of existing diagnostic imaging technologies for functional and anatomical imaging of eye has been presented. It has been observed that most of the current ophthalmic imaging modes suffer from issues, such as high cost, contact-mode, operator skill dependency, ionizing radiation, and high dependency on computationally intensive algorithms. Thus, it is desirable to have a highly accurate high resolution 3D non-ionizing, noninvasive, non-contact, patient-friendly anatomical and functional ophthalmic diagnostic imaging system that can be done in an ophthalmologist's office at a low cost. Initial investigation of a MEMS microwave sensor based UWB radar shows the promise to realize such a system.

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