BALKAN JOURNAL OF ELECTRICAL & COMPUTER ENGINEERING, Vol. 9, No. 2, April 2021

Reconstruction with In-Line Digital Holography Quantitative Phase Imaging for Tissue-Mimicking Phantom Samples

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***Abstract*—Optical imaging has attracted recent attention as a non-invasive medical imaging method in biomedical and clinical applications. In optical imaging, a light beam is transmitted through an under-test tissue by using an optical source. The beams which are gone through the tissue and/or reflected from the tissue surfaces are received by an array sensor. Based on the light intensity of these received beams on the sensor, sub-tissue maps are generated to scan large tissue areas so that any further biopsy is not required. Although the large tissue areas in pathological images can be scanned by using various methods, nonlinear deformations occur. To overcome this problem, the reconstruction process is frequently used.**

In this study, we propose an application of biomedical imaging based on performing the reconstruction of a phantom image via an in-line digital holography technique. Hence, many different sub-tissues can be imaged at the same time without the storage problem of the reconstructed image. To neglect the biopsy process required in medical imaging, the phantom image is obtained by using a linear array transducer for this study. We present the performance evaluation of the simulation results for the proposed technique by calculating the error metrics such as mean squared error (MSE), mean absolute error (MAE) and peak signal-to-noise ratio (PSNR). The obtained results reveal that the reconstructed images are well-matched to the original images, which are desired to be displayed by the holography technique.

Index Terms—**In-line digital holography, image reconstruction, optical imaging, phantom image.**

I. Introduction

IMAGING TECHNOLOGY is conventionally used both for the detection and localization of disease and mapping the anatomy of the human body. Hence, new medical imaging technologies that provide insight into the function, physiology, and metabolism of an organ have constantly been developed. These technologies are so crucial because the accurate diagnosis of diseases with advanced visuals are obtained by medical images and therefore, effective personal treatment options can be provided for all diseases. There are several commonly used types of medical imaging such as computed tomography (CT), mammography, positron emission tomography (PET), single photon emission computerized tomography (SPECT), magnetic resonance imaging (MRI) and etc. [1-3].

Differently from other medical imaging techniques such as x-rays, since visible light and photons are used in optical imaging, it is possible to achieve more detailed image versions of the body region of interest [4]. It also enables smaller structures such as cells and molecules to be visualized. For instance, biomedical optical imaging (BOI) methods are based on transferring a light beam through the tissue and collecting photons that escape from the tissue surface. In the BOI methods, the light beam is transferred through the tissue and the reflected beams are received by photo-detectors or cameras where the light intensity is measured by forming algorithms. The photons sent to the living tissue continue their travel between the organelles within the tissue cells (the largest of which is the nucleus organ) with diffraction through the cell membranes and absorption in the micro-molecules inside the cell, and the routes are determined as a result of these travels [4].

The obtained images with optical imaging can be used for the diagnosis and treatment of diseases by clinicians. In addition to imaging advantages, optical imaging also has several advantages in other respects [5]. One of them, and perhaps most importantly, is that the optical imaging decimates the harmful radiation to which the patient is exposed. Another one is that, unlike other imaging techniques, in optical imaging, many different features of an organ or a tissue can be seen and measured at the same time by using various light colors. All these advantages make optical imaging popular today. Thus, the studies in this area have increased tremendously for the last few years [6-13].

On the other hand, physical phantoms are used for clinical verification of current and newly developed medical imaging methods under different conditions. The validity of the imaging method is tested by performing various tests on the used phantoms such as geometric accuracy, dose algorithm

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Manuscript received November 23, 2020; accepted April 27, 2021.
DOI: 10.17694/bajece.829857

accuracy, image quality, machine and patient quality assurance, irradiation techniques [1, 14-16]. Therefore, the structure of the used phantom and the quality of the obtained medical image are important criteria to evaluate the performance of the imaging system. The solution to overcome these problems can be applying the image reconstruction process to the medical images via optical imaging. In addition, to obtain the three dimensional (3D) medical images, the reconstruction process is required where the series of images are sliced from a target sub-tissue [17-19].

A. Related Works and Motivation

In the literature, the sub-tissue images obtained by image reconstruction include the images of the sub-tissue microstructures although they cannot be seen directly with the human eye. [18, 19]. The sub-tissue maps are created with the light intensity values measured from the surfaces. On the other hand, the unnatural deformations of the anatomical structures are occurred resulting from the matching of the adjacent images. To remove the nonlinear deformation of the pathological images, the three dimensional (3D) reconstruction process is frequently used in the literature [17]. Kugler et al. proposed a non-rigid image registration method to reconstruct the 3D image of the microstructures in the tissue. They consider the smoothness of each constituent and the spatial continuity of the tissue [20]. Adler et al. reconstructed the post mortem MR images [21].

Digital holography is one of the methods to reconstruct the image in 3D [8]. In this context, Depeursinge et al. developed a method to observe the deformations and very small movements in excitable cells and tissue by using digital holography. This method allows determining the cells and morphology of the tissue [10]. However, in the mentioned studies of literature, the reconstructed images cannot be stored efficiently. To overcome this problem, holography technique can be used to reconstruct the image [8].

In the holography, the accurate three-dimensional (3D) imaging can be achieved by using the correct depth markings, without the necessity of specific imaging devices and strain of the eye [22, 23]. The 3D image which is recorded holographically can be reconstructed for visualization purposes. In addition to this, recording holographically have advantages in terms of storage since the obtained 3D information can be stored efficiently and encryptedly in holograms. Unfortunately, a long-time processing for the recording and a powerful laser source are needed for the traditional optical holographic recording process. This problem has been resolved in digital holography (DH) by using a digital camera for recording the media [8]. Because, after the phase and amplitude information of the object is recorded as digital in the CCD or CMOS cameras (recorded as a hologram), the object itself can be retrieved as digital by using reconstruction methods. On the other hand, instead of the photochemical procedures in traditional holography, the digital methods make the DH attractive in a wide variety of fields for science and technology.

One of the main features of the DH is that to be a full-field with high-resolution technique which records amplitude and phase information of the sample to be displayed. On the other hand, the optical field consisting of amplitude and phase information is measured in holography and interferometry while only the amplitude information is measured in conventional bright field imaging [24]. The cells and the tissues that are intended to be viewed medically have a transparent appearance when they are in the visible light zone. The phase information becomes beyond only a feature since there will be no good contrast in amplitude information when the samples are transparent. Because the transparent samples create a phase delay for the hologram records in the DH. In other words, when an optical wave passes through a transparent object with a thickness and refractive index, it experiences a phase delay which has detailed structural information about the sample [25]. Therefore, the phase information created by these phase delays is used in the DH while the images are reconstructed [26, 27].

The DH has enabled non-contact measurement of the cells and the tissues and their pathophysiological differentness [28]. Therefore, there have been various researches in literature related to the DH applications in the field of biomedical imaging, recently. Kim [29] has provided a review of the DH by examining its applications in the biomedical imaging. Furthermore, researchers have applied the DH to image various cell types such as red blood cells [30], fibroblast cells [31], diatom skeletons [32] and cancer cells [33].

B. Contribution

The main contributions of this paper is to apply the in-line digital holography technique for biomedical image reconstruction with different phantoms. Hence, the storage problem of the reconstructed image can be neglected by using digital holographic reconstruction process. Another one is that, many different sub-tissues can be detected at the same time. On the other hand, any further biopsy is not required when the created phantom image is used.

We present an application of biomedical imaging based on performing the reconstruction of a phantom image by using the in-line DH technique, which has been carried out with simulations by evaluating the image quality measurement. To this end, the hologram of the images obtained with a linear array transducer has been created with computer simulations by using the hologram recording and reconstruction senses in the DH. Thereafter, the phase information has been extracted from these holograms and the samples have been reconstructed in 3D. Based on the simulation results, the difference between the created phantom image and the reconstructed images are quite low. In this context, we reveal that using the DH reconstruction process with simulation and the phantom image is superior to conventional reconstruction techniques in terms of storage of reconstructed image and human health.

The rest of this paper is organized as follows: A summary of the formation of the used phantom image and the basic principles of in-line DH technique have been introduced in Section II. The Section III presents the obtained results and the superiority of the proposed technique has been revealed. Finally, the Section IV discusses the results and concludes the paper.

II. SIMULATION PROCESS

A. Image Formation

The data used in this study has been obtained by using a linear array transducer consisting of various transducers. By sampling with 128 beam lines at 40 MHz, the data has been collected in the sample where the sound velocity is 1540 m/s. Beam lines are 15 mm apart. One of the used phantom was formed by randomly inserting 5-43 μm glass beads scatters into the agar gel. Phantom images presented in Fig. 4a and 5a are created with simulation by applying logarithmic compression and histogram equalization methods in MATLAB program [34]. In addition, for the other one, a cylindrical phantom with two cylindrical fields that have similar sound velocities and a three-wire filament was used. The value of related parameters such as radius (r), speed of sound (c), density (ρ) and attenuation (μ) for the phantom is detailed in Fig.1.Thereafter, with the help of this known model data, the phantom image given in Fig. 6a is created by using MATLAB program [35].

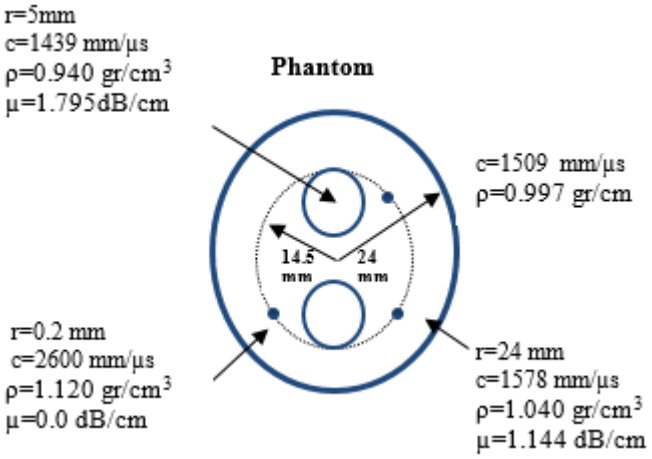


Fig.1. Phantom model used for created phantom [35]

B. Creation of the Hologram with Simulation

To create a hologram by simulation, the events that are the bases of the hologram recording should be expressed mathematically. Therefore, at this part of the study, the mathematical expressions used to create the hologram in in-line holography are provided. In this context, the methods of simulating holograms created with plane waves are described in Fig. 2. Thereafter, the original images of the samples are reconstructed from the created hologram [36].

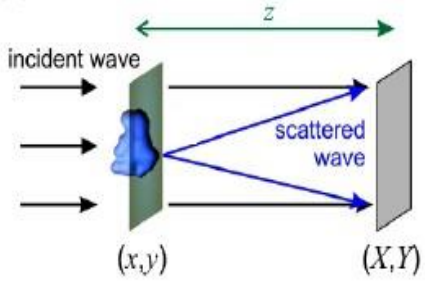


Fig.2. The scheme of in-line holography realized by using a plane wave [36]

Before describing the in-line holography, the description of the plane wave should be given. The plane wave defined by a distribution with complex-valued $\left(\exp\left(i\left(k_x x + k_y y + k_z z\right)\right)\right)$ has a constant phase value on all planes perpendicular to the wave propagation direction at time t. In an arbitrary timescale, $t = 0$ can be accepted to define the spatial distribution of the wave. In 3D space, $k = k_x, k_y, k_z$ is defined as the wave vector, and k_x, k_y, k_z are the vector components of this wave. Here, k is defined as the number of the waves ($k = \frac{2\pi}{\lambda}$). λ is the wavelength of the light [37].

Two plane waves called reference and object waves are used to create a hologram in in-line holography. The object to be recorded on the hologram and the beam which comes from the light source are in the same plane. While the wave that the beam generates by reflecting from the object is called the object wave ($O_{exit\_wave}(x, y)$), the reference wave ($R_{incident}(x, y)$) never touches the object along the plane. With the superposition of these waves, two light waves constitute an interference.

In this context, when the object position is set to $z = 0$ by selecting the origin of the z axis, the incident wave is given as

$$R_{incident(x,y)} = R_0 \exp\left(i\left(\varphi_1(x, y)\right)\right) = 1 \qquad (1)$$

This incident wave is called the reference wave ($R_{incident}$). Here, we can select the optical axis along the propagation of this plane wave to achieve $k_x = k_y = 0$ [36, 37]. In Eq. (1), (x, y) is identified as the coordinates of the plane.

On the other hand, the wave, whose information that will be recorded on the hologram and reflected from the object constitutes the object wave. This wave propagation is expressed mathematically with a transmission function (See Eq. (2)) as

$$\begin{aligned} O_{exit\_wave}(x, y) &= t(x, y) \\ &= \exp\left(-a(x, y)\right)\exp\left(i\varphi_2(x, y)\right) \end{aligned} \qquad (2)$$

where the absorption is defined as $a(x, y)$ and the phase distribution is given as $\varphi(x, y)$.

As mentioned above, the interference pattern created by the object and reference waves in the recording plane (X, Y) is given by the Fresnel-Kirchhoff diffraction formula given in Eq. (3). It expresses the propagated wave, which is spread from the object plane (x, y) toward the recording-CCD/CMOS camera plane (X, Y) [36].

$$U_{\text{detector}}(\mathrm{X},\mathrm{Y}) = \frac{i}{\lambda}\iint R_{incident}(x,y)\, t(x,y)\frac{\exp\left(ik\left|\vec{r}-\vec{R}\right|\right)}{\left|\vec{r}-\vec{R}\right|}\, d_x d_y \quad (3)$$

where the distance of the object plane (x, y) to the recording detector plane is given as $\left|\vec{r}-\vec{R}\right| = \sqrt{(x-X)^2+(y-Y)^2+z^2}$. In this expression, the constant phase is neglected.

Hologram simulations based on the creating hologram with mathematical expressions consist of the following steps:

1. Firstly, the object to be created hologram should be imread.
2. Secondly, the coordinate axes should be determined and the imread object should be placed on the coordinate axes.
3. Thirdly, once the reference coordinates are also determined, the created hologram should be placed on the coordinate axes.
4. Finally, by using the Eq. (3), the interference pattern should be calculated.

In order to reconstruct the sample object from the hologram created by simulation and to extract the phase information, Fourier transform algorithm (FTA) is used in this study [36, 38, 39]. Therefore, to find the phase information and to reconstruct the object, the following processes should be implemented.

a) Fourier transforms of the holograms are taken line by line.

b) An appropriate filtering is done to separate the real and virtual images. This filtering is applied by spatially in the Fourier domain.

c) With this process, the maximum frequency point where the phase is collected can be found. Hence, it will be filtered since it is the virtual region after the half of the amplitude and phase sequences.

d) Finally, the phase of the hologram is obtained by taking the inverse Fast Fourier transform (IFFT) line by line.

III. SIMULATION RESULTS

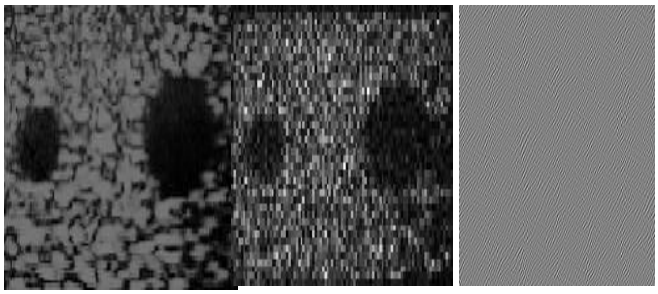
In this study, the used phantom image, created by randomly inserting glass beads scatters, has been obtained by using a linear array transducer. Thereafter, the holograms of the acquired images have been produced by simulations and the real phantom images have been extracted from the phase information of these images with the reconstruction process.

As a first step, instead of the obtained phantom images, the hologram of the words "phantom created with glass bead", written in paint program, has been created by simulation. The phase information has been extracted from these holograms to retrieve the original text. The original, the reconstructed and the hologram images for the used text "phantom created with glass bead" are presented in Fig. 3, respectively.

a b c

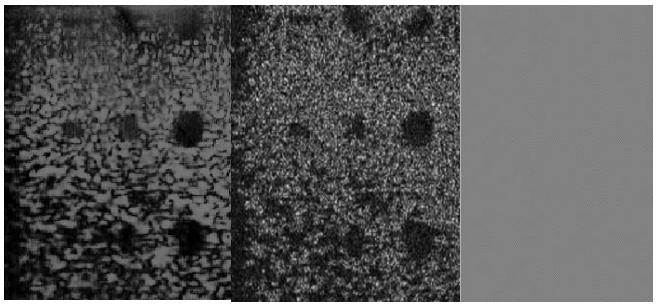
Fig. 3. Simulation results; a) Original text created in paint program; b)Reconstruction of the original text; c) Hologram of the original text structure

For the second stage of the study, a hologram has been created from the images of the phantom which is formed by randomly inserting glass beads scatters into agar gel and viewed by a linear array transducer. Then, the phase information has been extracted from these holograms to reconstruct the original phantom image as stated in the first step. The obtained results for three different phantom images are presented in Fig. 4, Fig. 5 and Fig. 6, respectively.



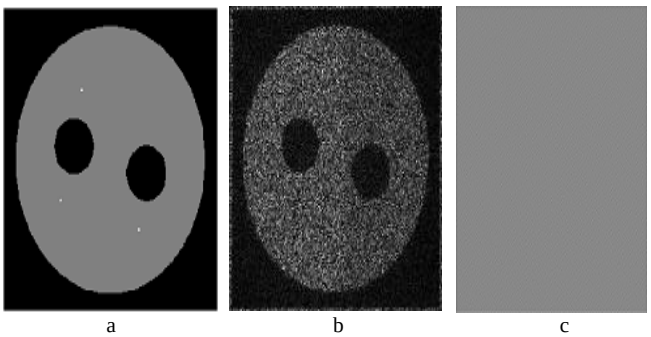
a b c

Fig. 4. Simulation results; a) First image of the used phantom b)Reconstruction of the first image c) Hologram of the first image



a b c

Fig. 5. Simulation results; a) Second image of the used phantom b)Reconstruction of the second image c) Hologram of the second image



a b c

Fig. 6. Simulation results; a) Third image of the used phantom [35] b)Reconstruction of the third image c) Hologram of the third image

Finally, the differences between the used original images whose holograms to be created and the reconstructed images by using the phase information of the hologram have been revealed by the mean squared error (MSE), mean absolute error (MAE) and peak signal-to-noise ratio (PSNR) which are the most common predictors of image quality measurement and calculated by using the equations given in Eqs. (4-6) respectively [40-42].

$$MSE = \frac{1}{mn}\sum_{i=0}^{m-1}\sum_{j=0}^{n-1}\left(I(i,j)-K(i,j)\right)^2 \tag{4}$$

$$MAE = \frac{1}{mn}\sum_{i=1}^{m}\sum_{j=1}^{n}\left|\left(I(i,j)-K(i,j)\right)\right| \tag{5}$$

$$PSNR = 10\log_{10}\frac{\left(2^n-1\right)^2}{\sqrt{MSE}} \tag{6}$$

where m and n are the numbers of the rows and columns of the images (size of the images), i and j are the indices of the pixel values which are investigated in the images. I and K are the original and the reconstructed images, respectively. The comparison of MSE, MAE and PSNR quality measurements values for the used original images are given in Table I [40], and the calculation of these metrics between the used images to create the holograms and the reconstructed ones are presented in Table II.

TABLE I
MSE, MAE AND PSNR VALUES FOR ORIGINAL IMAGES [40]

Original Image Values		
No	**The Parameter of Quality Measurement**	**Quality Value**
1	MSE	0
2	MAE	0
3	PSNR	∞

TABLE II
MSE, MAE AND PSNR VALUES OF THE USED AND RECONSTRUCTED IMAGES

Used Image	**MSE**	**MAE**	**PSNR**
Original text created in paint program	0.0226	0.0511	116.1410
First image of the used phantom	0.0400	0.0925	92.0757
Second image of the used phantom	0.0307	0.0803	103.6434
Third image of the used phantom	0.0181	0.0587	126.5263

It can be seen from Table II, consistent results are found for all used images in terms of MSE and MAE since the closer to zero values are achieved which are the better performance in terms of MSE and MAE reference metric [40,41]. Moreover, the indication of the higher quality for the reconstruction is generally a higher PSNR value. The results obtained for all used phantom images are in the desired levels in terms of PSNR values.

IV. CONCLUSION AND DISCUSSIONS

The BOI has become a developing imaging technique with the DH imaging. In other medical imaging techniques, small lesions, masses, or the structure of existing masses in the investigated tissue or organ are often undetectable. This situation causes delays in diagnosis and treatment phases. Also, in these methods, it is mostly sent to pathology at the detection stage and either by passing through a set of biochemical agents which is called staining or after cutting the tissue directly, it is cut into slices and displayed under a microscope. Cells are examined histopathologically by staining with biochemical agents.

The reason for the examining under microscopy is to understand what tissue cells look like and if the carcinogen ones are malignant or benign to understand its kind and diagnose accordingly and to initiate treatments. Since both phase and amplitude information can be recorded and the object itself can be retrieved without any loss of information from these in digital holography, the presence of these cells can be diagnosed in tissues and similar cells without the need for pathological examination and the treatment process can be accelerated. In addition, the ability to obtain detailed images without exposure to excessive radiation makes the imaging technique superior to other similar methods.

Tissue mimicking phantoms have a wide range of biomedical applications in the field of various techiques such as, Raman spectroscopy, digital holography, acoustic waves imaging, photoacoustic imaging, holographic tomography microscope (HTM) and etc. (Table III). Most of the mentioned applications are used to analyze the characterization of the phantoms whereas some of them are used to investigate the reconstruction process of many different tissue types. A comparison of this work with existing studies in the literature are given in Table III.

For instance, Chaiken et al. evaluate the system for the detection of glucose in blood by using tissue modulated Raman spectroscopy [43]. Hydrogel is used for tissue model. They also discuss the variations between the spectra human blood in vitro and their noninvasively measuring spectra. Raman spectroscopy is also used by Vardaki et al. to review the biomedical applications for the types of tissue phantoms that are created as liquid phantoms [44]. Shiguang et al. produce the homogeneous and two-layer soft-tissue phantoms to map the elasticity inside soft tissues. They perform their study by using digital holography and surface acoustic waves imaging [45]. Karaböce et al. detect the positions of objects inside the phantom that created with agar gel. The Sonix Touch Q +" ultrasonic device and different types of probes are used to verify the image processing and measurement in this study [46]. Maneas et al. introduce the gel wax-based tissue-mimicking phantom for imaging with photoacoustic. The acoustic and optical characterizations are investigated on homogeneous phantoms [47].

TABLE III
RELEVANT STUDIES DEALING WITH BIOMEDICAL APPLICATIONS FOR THE TYPES OF TISSUE PHANTOMS

Authors	Simulated tissue/ purpose of the study	Used method	Phantom type
Chaiken et al (2001)[43]	To evaluate the system for the detection of glucose in blood	Raman spectroscopy	Hydrogel
Shiguang et al. (2011)[45]	To map the elasticity inside soft tissues	Digital holography and surface acoustic waves imaging	Homogeneous and two-layer soft-tissue phantoms
Karaböce et al. (2017) [46]	To verify the measurement results of different objects in tissue-mimicking phantom	Sonix Touch Q +" ultrasonic device and different types of probes	Agargel
Maneas et al. (2018) [47]	To introduce the gel wax based tissue-mimicking phantom	Multispectral photoacoustic imaging	Gel wax
Pichat et al. (2018)[18]	To review the 3D histology reconstruction methods for many different types of tissue	3D histology reconstruction methods	Liquid phantoms
Ziemczonok et al. (2019) [48]	To characterize the performance of a limited-angle HTM by using phantom	Holographic tomography microscope (HTM) and tomographic reconstruction analysis	Manufactured by 3D laser photolithography
Kugler et al. (2019) [17]	To propose a reconstruction method for pancreatic cancer tumors obtained from histopathological images	Non-rigid 3D reconstruction method	-
Vardaki et al. (2020)[44]	To review the biomedical applications for the types of tissue phantoms	Raman spectroscopy	Liquid phantoms

In these studies mentioned above, the reconstruction process is not evaluated. However, in order to eliminate the storage problem when the investigated images take the big space, the reconstruction process can be required. In this context, Pichat et al. performed a survey about 3D histology reconstruction for many different types of tissue that are created as liquid phantoms [18]. They first summarise the digitised process from a tissue specimen, and then to overcome the storage problem, they describe the 3D histology reconstruction process where the 3D medical imaging is used or not. On the other hand, Ziemczonok et al. characterized the performance of a limited-angle holographic tomography microscope by using phantom manufactured by 3D laser photolithography. A full reference image quality assessment metric which is given such as the universal quality index Q, is applied to the tomographic reconstruction process [48]. In addition, to reconstruct the 3D image of the microstructures in the tissue, Kugler et al. used a method of non-rigid image registration. They remove the nonlinear deformation of the pathological images and investigate the smoothness of each spatial continuity of the tissue [17].

To the best of authors' knowledge, the reconstruction of tissue mimicking phantoms imaging with digital holography is very limited in the literature. In addition, there has been no work which considers reconstruction process performed by using in-line digital holography and evaluated in terms of image quality measurement [40] for reconstructed phantom images, yet. In this context, biomedical image reconstruction is performed with in-line digital holography in order to eliminate the storage problem for many different types of tissue in 3D medical imaging. Moreover, the obtained reconstructed images are evaluated in terms of image quality measurement to validate the study as a strong work.

As mentioned in Section II, hologram recording has been performed with a simulation study based on in-line digital holography for a text created in paint (paintbrush) as the first stage and for phantoms formed by randomly inserting 5-43 μm glass beads scatters into the agar gel and scanned by a linear array transducer as the second stage. The reconstructed process is performed by using FTA.

In order to examine the validity of the study, the difference between the original image recorded with the hologram and the image reconstructed with this technique has been obtained by calculating the error metrics. Because, the assessment of image quality is closely related to the assessment of the image similarity. Sasi Varnan et al. defined the quality measurement parameter and their corresponded value [40]. For this context, MSE, MAE and PSNR values are calculated for each obtained results and evaluated based on [40]. These results are presented in Table II.

As it can be clearly seen in Fig. 3-6, the reconstructed images provide consistent results with the original images that are desired to be displayed by holography technique. The MSE values for the images of original text created in paint program, first image of the used phantom, second image of the used phantom and third image of the used phantom are obtained as 0.0226, 0.0400, 0.0307 and 0.0181, respectively. These results are closer to zero, which are expected values based on [40]. This means that the similarity between the original and the reconstructed image has maximum value. On the other hand, the MAE values obtained for the images given in Fig. 3-6 are calculated as 0.0511, 0.0925, 0.0803 and 0.0578, respectively. According to the results, the differences between the original and reconstructed images are quite low like as MSE values. As for the PSNR values, it is expected that these values are closer to ∞ and quite high. In this study the PSNR values are obtained as 116.1410, 92.0757, 103.6434 and 126.5263 for the investigated images, respectively. These results supply the expectations (Table I).

In the light of the results obtained in this study, it can be concluded that the neglection of the storage problem for the reconstructed images and making possible to image many different sub-tissues at the same time can be provided by in-

line digital holography. Because, the reconstructed images are obtained with high image quality. Moreover, the use of a phantom image eliminates the necessity of the biopsy process in medical imaging.

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