PERSPECTIVE ON USING TALBOT-LAU X-RAY PHASE CONTRAST IMAGING FOR ATHEROSCLEROSIS DIAGNOSIS

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X-ray Phase Contrast Imaging based on refraction of radiation is a promising approach for better visualization of materials with low Z, such as tissue, providing high quality images with enhanced contrast and very high spatial resolution. The refraction coefficient for materials with low Z is much larger than the attenuation one, so this provides the possibility of detecting fine structures in the human body, such as lipidic and fibrous deposits. In this paper, we present a possible method to identify atherosclerotic disease in the early stages, in principle, the cholesterol crystals or atheroma from the artery wall, which leads to plaque formation, one of the main reasons for thrombosis or ischemic stroke.

Keywords: phase contrast imaging, grating interferometry, Talbot-Lau, artery imaging, cholesterol crystals, atherosclerosis.

1. Introduction

Atherosclerosis is one of the leading causes of mortality and morbidity in developed countries. In essence, it reduces the vascular lumen by deposition of lipids in the blood vessel walls, forming atheroma plaques, which reduces blood supply to tissues, causing ischemic suffering [1]. The diagnosis of this disease with conventional imaging techniques (angioscopy, ultrasounds, computed tomography, magnetic resonance imaging, positron emission tomography) is still challenging for physicians because of low soft tissue contrast, limited accuracy, insufficient spatial resolution, and also a very high cost [2]. In this context, X-ray Phase Contrast Imaging (PXI), which is an approach based not on the absorption of X-rays but on their refraction, providing high quality images with a combination of high spatial resolution and enhanced contrast for materials with low Z, such as tissue and biological materials, could be a method for identification in early stages of atheroma or cholesterol crystals, to avoid the complications of atherosclerosis and all the

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characteristics associated with this condition. Another major strength of this technique is that it provides more than one type of image contrast. The contributions of attenuation, refraction, and scattering to the X-ray signal can be separated, and three different images are obtained: the conventional attenuation image describing the X-ray attenuation in the object, the refraction image depicting differential density variations (gradients), and the scattering image describing density variations on the μm scale. The refraction image strongly enhances the edges of the object. This can be useful to highlight boundaries of tumors or lesions, for instance. An additional image is obtained by numerical integration of the refraction image, which describes with high sensitivity small density differences in the bulk object. Phase contrast computed tomography has been explored for atherosclerotic plaque characterization in an experimental ex-vivo study by Holger Hetterich *et al*. The results show that phase contrast tomography can discriminate the critical components of vulnerable plaque, such as the lipid-rich core, the fibrous cap, and calcifications [3]. The present work shows that even simple phase contrast radiography, without tomographic reconstruction, has the potential to detect plaque calcification, lipids, and possibly cholesterol crystals.

2. Fundamentals of the method

Since the discovery of X-rays by Wilhelm Conrad Röntgen in 1895, they have become a valuable tool for materials structure analysis. Most of the studies are based on the corpuscular properties of X-rays. However, the interaction of X-rays with matter can be characterized by the wave formalism, where the complex index of refraction can be defined:

$$n = 1 - \delta + i\beta \tag{1}$$

where δ is the refractive index decrement which gives the phase shift of the wave, and β is the absorption index.

Considering a plane wave propagating in the z direction, in vacuum:

$$\Psi_v(\vec{r},\, t) = Ae^{i(\vec{k}\vec{r}-\omega t)} = Ae^{i(kz-\omega t)} \tag{2}$$

after the wave is passing through a material with refraction index $n = 1 - \delta + i\beta$, it becomes:

$$\Psi_m(\mathrm{z},\, t) = Ae^{i(nkz-\omega t)} = Ae^{-i\omega t}e^{(1-\delta)ikz}e^{-\beta kz} = \Psi_v\,(\mathrm{z},\, t)\cdot e^{-i\delta kz}\cdot e^{-k\beta z} \tag{3}$$

where the first exponential term describes the change in phase, and the second represents the attenuation. So, after traveling through a medium with thickness z, the wave amplitude and wave phase of the exit wave are modified by a factor $e^{-k\beta z}$ and respectively, $e^{-i\delta kz}$. A varying phase shift of the X-ray wave causes a refraction of the beam by an angle α (of the order of micro-radians) in the direction perpendicular to the propagation direction. The angle is related to the first derivative of the phase shift $\partial\Phi/\partial x$ by:

$$\alpha_x = \frac{\lambda}{2\pi}\frac{\partial \Phi}{\partial x} \tag{4}$$

where Φ is the phase shift coefficient and $\Phi = 2\pi\delta/\lambda$.

In the range of medical imaging X-ray energies (20-100 keV), the refractive index, δ, is larger than the absorption index, β, by almost three orders of magnitude. Additionally, δ is decreasing more slowly with energy than β: $\delta \propto 1/E^2$ and β∝ $1/E^4$, so this technique offers the possibility to obtain higher soft tissue contrast images by using the phase shift of X-ray radiation. For instance, in the case of 30 keV photons, $\beta/\delta \sim 10^{-5}$ in beryllium (Z = 4), $\beta/\delta \sim 10^{-4}$ in tissue and $\beta/\delta \sim 10^{-3}$ in calcium (Z = 20) – calculated with XOP (X-ray Optics utilities) [4]. Until now, the researchers developed different techniques to bring out the best of these properties, to increase the contrast and reduce the dose for the patients. The main methods developed are: crystal interferometry, propagation-based imaging, and grating interferometry. Each of these methods has advantages and disadvantages, and they are different from the point of view of the experimental set-up, results, and requirements of X-rays [3]. The propagation method does not require optical X-rays elements, and the contrast image is proportional with the second derivate of phase shift; in the case of crystal interferometry and gratings interferometry, the contrast image is proportional with the first derivate of the phase front, being thus more sensitive to bulk density variations. Because the refraction angle is very small, of the order of micro-radians, one needs X-ray optics to analyze such small deviation. A method that allows coping with this problem is the grating interferometry with Talbot-Lau interferometer [5].

The Talbot-Lau interferometer is composed of 3 micro-periodic gratings: two absorption gratings and one phase grating. The first absorption grating – the source grating is placed near the X-ray source, and it has the role of transforming the source into a coherent one. It creates an array of individually coherent but mutually incoherent virtual sources of smaller dimensions. The phase grating is typically a silicon or a nickel grating, and it creates a pattern of interference through the Talbot effect. Talbot effect occurs when a periodic structure is coherently illuminated, and an interference pattern is created. Practically an image of the structure is formed, and it is repeated at regular distances. This regular distance is called Talbot distance, and it depends on the periodicity p of the object and the X-ray wavelength λ.

$$d_T = m\frac{2p^2}{\lambda} \tag{5}$$

where m is the Talbot order; it should be odd because phase gratings produce fringes with maximum contrast only at odd Talbot orders, typically 1 or 3.

Because the pattern is too fine to be resolved by conventional X-ray detectors (having pixels of several tens of microns typically), a third absorption grating is used – analyzer grating, at a fractional talbot distance from the phase grating, which transforms the local fringe displacements into signal intensity variations.

3. Experimental set-up

The experiment presented in this paper was carried out at Johns Hopkins University, Department of Physics and Astronomy (Baltimore, USA). The purpose of this experiment was to demonstrate the ultrahigh sensitivity of phase contrast X-ray imaging at 20-40 keV (medical clinically relevant energies) as a new method for atherosclerosis identification and also to open the way towards laser-based medical imaging. The set-up used was a symmetric Talbot-Lau interferometer, operated in 27th Talbot order, with three gratings of 2.4 μm period and a polychromatic source. The distance between the source and the sample was approximately 95 cm and between the sample and the detector about 85 cm. The gratings used in this set-up were produced by Microworks GmbH using lithography and electroplating. The details of the gratings can be seen in Table 1. and Fig. 1. The high performance of a Talbot-Lau interferometer relies on gratings quality and parameters. The characteristics of the gratings are limited by the fabrications and technological considerations and were chosen as a compromise between high angular sensitivity and a good spatial resolution. The angular sensitivity, which is defined as the smallest refraction angle that can be measured, can be improved using smaller gratings periods or increasing the propagation length of the X-ray by increasing the distances between gratings and is maximum in a symmetric Talbot-Lau set-up (having gratings of equal period and equal distances between gratings) [6]. In particular, the two absorption gratings should stop the energetic X-ray photons, so a thickness of at least 25–30 μm of a high atomic number element, such as gold, is required. For the moment, because of the technological constraints, the period of 2.4 μm is the maximum that can be achieved with a thickness of approximately 60 μm of gold.

Table 1.

Parameters of the gratings used for Talbot-Lau Interferometer for artery radiography

Type	Material	Period (μm)	Height (μm)
Source Grating	Gold	2,4	55
Analyzer Grating	Gold	2,4	57
Phase Grating	Nickel	2,4	8,6

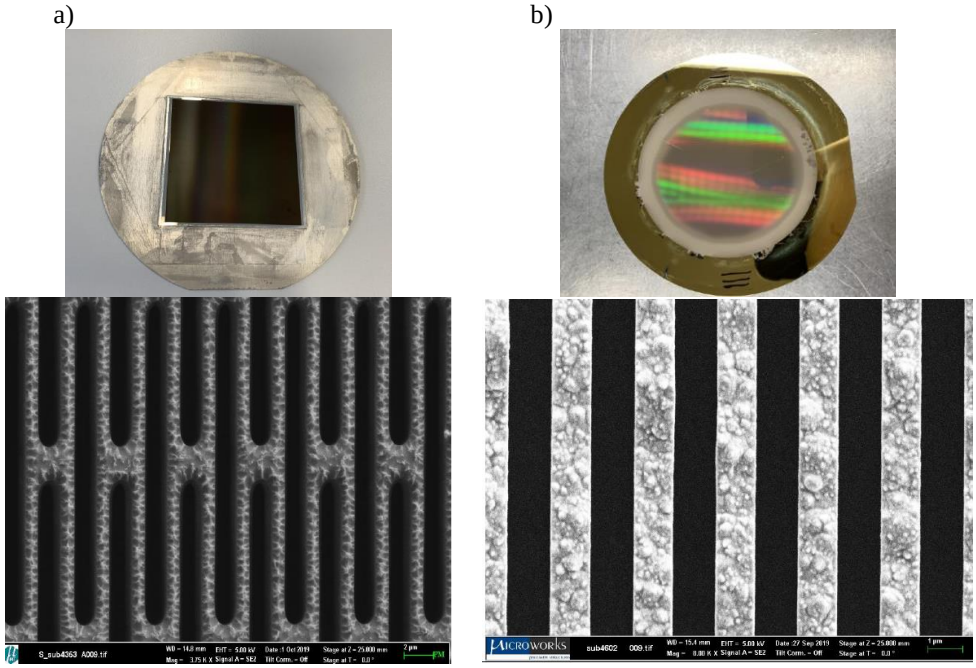


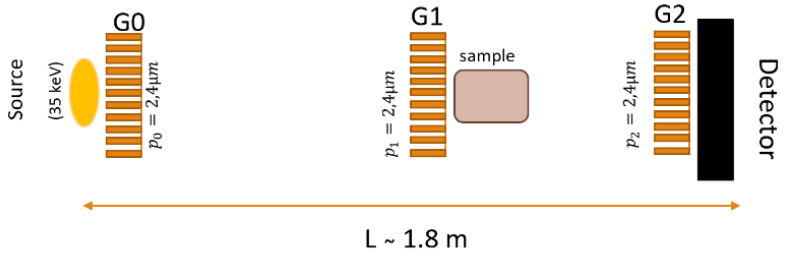
Fig. 1. High Sensitivity micro-Gratings: a) absorbing gratings - high sensitivity gold gratings of 50x50 mm area. The sensitivity of the interferometer comes from a very small period. The accuracy of the gold bars is better than 0.1 μm. b) phase grating - 8.8 μm nickel thickness.

The X-ray tube was operated at 35 kVp, and the emitted radiation was filtered with 1 mm of aluminum and 65 μm copper to cut out the low energies that are not relevant for medical examination but contribute to a higher dose of radiation. The resulting X-ray spectrum was calculated by the SpekCalc program [7], [8], [9] and had the mean photon energy around 25 keV, the designed grating energy. The detector was placed directly behind the analyzer grating, and it consists of a CCD Camera with 9 μm pixel dimension, a columnar CsI scintillator screen 50x50 mm, 150 μm thick, and a high numerical aperture lens resulting in a high detector quantum efficiency (DQE).

The sample used was an atherosclerotic iliac artery immersed in a 20 mm diameter tube filled with formalin to approximate imaging of the artery in the body. This set-up also avoids strong phase variations at the boundary between the tissue, air, and the plastic container. A 2 mm diameter soda straw was used as a spatial and phase resolution reference object. A picture of the experimental laboratory set-up is shown in Fig.2b. As for the data collection and analysis method, we used the phase stepping technique. The phase stepping method is used to sample the interference pattern at different relative grating positions and to retrieve three separate images (attenuation, phase, and scattering). It consists of moving one of the three gratings laterally in steps of a fraction of the period, perpendicularly to the beam direction. The phase stepping method gives rise to intensity modulations in

each pixel. These nearly sinusoidal modulations can be analyzed by Fourier methods to separate the attenuation contribution from the refractive and scattered components to the images [10]. In this case, the phase grating G1 (see Fig. 2a) was scanned laterally by sixteen steps over one period of the interference pattern created by the grating.

a)



b)

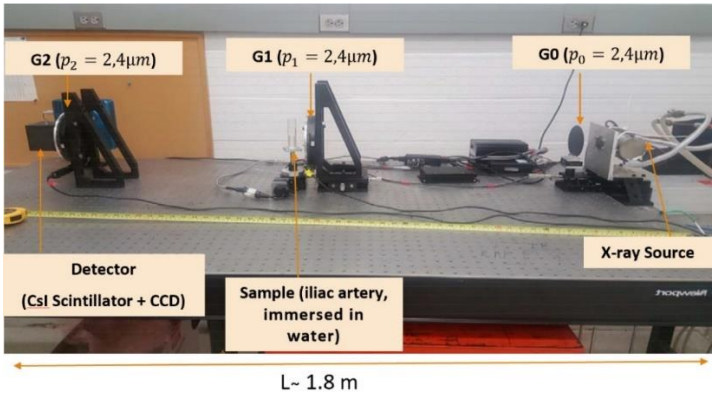


Fig. 2. a) Schematic representation of Talbot-Lau set-up used in the experiments for medical energies (20-40 keV). b) Photo of high sensitivity 1.8 m long interferometer with 2.4 μm gratings and 27th Talbot order built at Johns Hopkins University laboratory.

4. Results and discussion

The obtained results are shown in Fig. 3. As discussed in the previous chapters, we obtained three images: conventional attenuation (a), PXI phase (b), and PXI scattering (c).

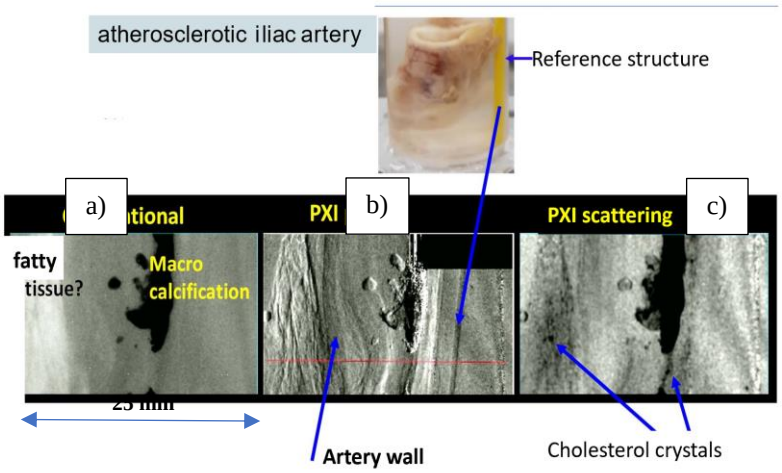


Fig.3. Attenuation image, PXI phase image, and PXI scattering or dark field image of an atherosclerotic iliac artery sample in formalin obtained with the Talbot-Lau set-up.

In the attenuation or conventional image (a), there are no details observed about the structure of the artery walls or the reference structure; it shows only lipid tissue and macrocalcification due to the plaque. On the other hand, in the PXI phase image (b), the structure of artery walls, the reference structure, and the macrocalcifications are well defined. The X-ray refraction angles measured are very small, of the order of 0.1 micro-radians. The third image, the PXI scatter, shows, besides macrocalcification, some small structures in the fatty mass and on the artery wall. These small structures visible just in PXI scatter image are thought to be cholesterol crystals, an early indication of thrombosis and atherosclerosis. As opposed to calcifications, these structures appear only in the dark-field image and not in the attenuation one, indicating that they are composed of a micro-structured low Z substance. Thus, the method that we propose in this paper could enable screening for early detection of this widely spread medical condition.

Another major point of this paper is that it demonstrates the capability of the Talbot-Lau interferometer to operate in a very high Talbot order for high angular sensitivity (a few micro-radians). In general, this type of instrument is used in low Talbot orders, first or third, because when using a spectrally broad X-ray source such as a W anode tube, the width of the spectral region of high contrast decreases as 1/m [5] with the mention that in high order configuration, when m is much bigger than 1, the bands became very narrow and when average over the typical broad X-ray spectrum the contrast is still good for imaging. So, an optimal choice for this interferometer's high performance should simultaneously consider the interferometer length, the grating periods, the Talbot order, and the source size.

The results also indicate that to further increase the interferometer's sensitivity, we have to increase the interferometer length, but unfortunately, this cannot be done with conventional X-ray tubes because of low photon flux at long

distances. Long interferometer length experiments are already done at synchrotrons, but these X-ray sources are too expensive and large for practical and clinical applications. In order to fully benefit from the advantages of phase contrast imaging, we need to use new sources, more compact and with a lower cost, but still spatially coherent like the synchrotron. High power lasers offer this possibility [10], [11], [12], [13]. The intense electric field produced by lasers instantly accelerates electrons in the matter to ultra-relativistic energies (of the order of GeV), and at the same time, their trajectory is oscillated by local microscopic fields producing intense X-rays. Due to the ultra-relativistic speed of electrons, the radiation is emitted in a narrow cone, similar to the synchrotron emission. In low-density plasmas, this process is called laser wakefield acceleration (LWFA), and it produces through a mechanism called betatron emission, X-ray sources with a focal spot of 1-2 μm, with spatial coherence at least as good as that of synchrotrons [14] [15]. The research directions at ELI-NP include the development of laser-plasma betatron sources and the medical applications of PXI with these sources.

5. Conclusions

In conclusion, the experiment performed at Johns Hopkins University with an interferometer designed for an energy of 25 keV and having visibility around 27% demonstrated high sensitivity of phase contrast imaging and the potential of PXI for arterial plaque diagnostic. The sample used was an atherosclerotic iliac artery, and the results obtained indicate an improvement in visualization of the components that conduct to the formation of plaque and, furthermore, to ischemic stroke. All these results demonstrate the high potential of this method for medical applications and open the way for phase contrast imaging with laser-created X-ray sources. Better results are expected with a betatron X-ray source with energy in the range of 20-40 keV and a several meters long laser-based set-up having only beam-splitter and analyzer grating – the Talbot method, which will increase the sensitivity and fringe visibility of the technique significantly.

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