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X-ray phase sensitive imaging methods: basic physical principles and potential medical applications

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Abstract

Phase sensitive imaging theoretically allows for a drastic reduction in x-ray dose while simultaneously achieving comparable or better spatial and contrast resolution compared to traditional x-ray absorption based imaging. Several techniques exist to extract the phase information from an x-ray signal, including x-ray interferometry, diffraction enhanced imaging, in-line holography, coded aperture x-ray imaging, and grating-based interferometry. The physics of each method is reviewed, along with the potential clinical applications.

Keywords

CT; phase contrast; DEI; in-line holography; x-ray interferometry

Introduction

X-rays have been widely used in medical imaging since their discovery in 1895. These relatively energetic photons interact with tissues that have different attenuating properties to generate contrast for visualization of the difference between tissues[1, 2]. Microscopically, the interaction between x-ray photons and tissue is described by different cross sections of physical processes such as photoelectric, Compton scattering, and others. In the diagnostic x-ray energy range (10keV–150keV), the photoelectric effect is predominant for contrast resolution, while the other physical processes only contribute to degrade image quality. The relative contrast between two tissue types drops quickly with increases in x-ray beam energy. However, when the x-ray beam energy is too low, the deposition of x-ray energy in tissues increases, and harmful radiobiological effects may occur. Thus, a delicate balance between the contrast needed for medical diagnosis and the potential detrimental effects of x-ray deposition must be achieved for x-ray-based medical imaging. Often, additional contrast is needed past the limitations of radiation dose constraints. To improve contrast resolution, external iodinated contrast agents are often administered either through an intravenous or intra-arterial injection. This has been proven to be extremely powerful in vascular imaging where a subtraction can be applied to remove the static anatomic background (also called “anatomic noise” in the literature) while the iodine-filled vasculature remains after the subtraction.

To improve contrast resolution such that the local difference between two neighboring local regions of tissues could be better differentiated in medical diagnosis, x-ray computed tomography (CT) was introduced in the 1970s. In this method, projection information is

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acquired from many different view angles and the local distribution of the x-ray attenuation coefficients is reconstructed. The introduction of CT methods significantly enhanced physicians' capabilities in medical diagnosis. However, similarly to the conventional x-ray projection method, the requirement of lowering radiation dose favors higher energy beams, but at the cost of a decrease in contrast resolution.

In addition to the balance between contrast resolution and radiation dose, when high spatial resolution is needed for visualization of fine structures, the noise level of both x-ray projection and CT imaging increases dramatically. In order to maintain the required contrast-to-noise ratio (CNR) for visualization of differences between tissues, a high radiation dose is required to compensate for the increase in noise level.

Even if x-ray CT is used, the characterization of tissue type is still not completely quantitative. The ambiguity lies in the fact that different tissue compositions may generate exactly the same attenuation [3]. This is because the attenuation properties are determined by both electron density and the effective atomic number.

Since its conception, x-ray imaging has been successfully used in medical diagnosis, but the sole contrast mechanism, x-ray absorption, significantly limits wider and safer applications. An ongoing goal in the use of x-rays in medical applications is to have the lowest possible radiation dose, while maintaining the highest possible spatial and contrast resolution, in addition to having quantitative imaging capabilities.

The limitation of a single contrast mechanism in x-ray imaging has motivated investigators to explore the possibility of multiple contrast mechanisms. As a result of wave-particle duality, x-ray beams can also be viewed as waves. The only difference from the familiar wave examples is that the x-ray wavelength is very short, on the order of angstroms. Due to their wave nature, x-rays will not only be attenuated when they penetrate through matter, but will also experience distortions due to the interaction of the wave with the particles inside of the medium. As a result, a local phase shift will be generated in the x-ray wave after exiting the object. Physically, local phase shifts of x-ray waves are determined by the local electron density in the object. Namely, when x-rays propagate through matter, the internal structural information of the material is encoded into the corresponding wave front distortions. Thus, by detecting the wavefront distortion in x-ray waves, one may potentially obtain the structural information of an object. Several methods have been used to extract wave front distortion; these methods are collectively referred to as x-ray phase sensitive imaging methods.

In this article, we intend to provide a concise review of the methods used to extract phase shift, with an emphasis on potential application in medical fields. However, one should be aware that the same concepts and methods can be equally applied to non-destructive detection in industrial and other applications. When those applications are considered, the relative advantages and limitations of each method may be very different.

Basic physics of phase sensitive imaging

When a wave is considered, one is reminiscent of the macroscopic phenomena observed in visible light: reflection and refraction at the interface of two different media, as well as diffraction and interference. To describe these phenomena, a medium is often considered as homogeneous sub-regions with sharp boundaries, with each sub-region having its own macroscopic refractive index, n . By definition, vacuum should not affect the wave and thus has a refractive index of unity. For visible light, the refractive index is often larger than one. For example, the refractive index of visible light in glass ranges from about 1.5 to 1.8 [4]. This large refractive index makes the observation of reflection and refraction of visible light

easy in normal laboratory conditions. In contrast, for x-rays, the refractive index is much closer to unity, with the difference from one often being only 10^{-7} to 10^{-5} . As a result, it is very difficult to directly observe x-ray refraction phenomenon. In general, the refractive index for x-rays is written as [5]:

$$n=1-\delta+i\beta, \quad (1)$$

where δ is the refractive index decrement, which is responsible for x-ray phase shift, and the imaginary part, β , is responsible for x-ray attenuation. The refractive index is a dimensionless quantity and its imaginary part, β , is related to the conventional linear attenuation coefficient, μ , as follows:

$$\mu=\frac{4\pi\beta}{\lambda}, \quad (2)$$

where λ is the wavelength of the x-ray. The decrement and the imaginary part of the x-ray refractive index are given as:

$$\delta=\frac{\rho_e r_e \lambda^2}{2\pi}, \quad (3)$$

$$\beta=\frac{\rho_e \lambda}{4\pi Z}(\sigma_{pe}+\sigma_c), \quad (4)$$

where ρ_e is the electron density and $r_e=2.818\times 10^{-15}$ m is the classical radius of the electron, Z is the atomic number, and σ_{pe} and σ_c are the photoelectric and Compton scattering cross sections, respectively. Since the photoelectric cross section decreases with energy, E , faster than E^{-3} , the imaginary part of the refractive index decreases with energy faster than E^{-4} . In contrast, the decrement of the refractive index only decreases with energy as E^{-2} .

The magnitude of the phase shift within a homogeneous medium is determined by the decrement of refractive index of the medium, δ , and the thickness of the medium [5]. An inhomogeneous medium can be treated as many homogeneous media with infinitesimal thickness and thus, the total amount of x-ray phase shift generated by an inhomogeneous object is given by [1, 5, 6]

$$\phi=\frac{2\pi}{\lambda}\int_{\ell} dl\delta(l)=\lambda r_e\int_{\ell} dl\rho_e(l) \quad (5)$$

where the integral is taken over the x-ray path length. Thus, the phase shift is uniquely determined by the distribution of electron density. This is in stark contrast to the imaginary part, and the related linear attenuation coefficient, which is dependent on both electron density and atomic number, as shown in Eq. (4). The line integral of electron density expressed in Eq. (5) is reminiscent of the attenuation of x-rays when they penetrate through a non-uniform medium. In the attenuation case, the logarithm of the ratio of entrance and exiting photon numbers gives a line integral of linear attenuation coefficient:

$$\ln\frac{N_0}{N}=\int_{\ell} d\ell\mu(\ell). \quad (6)$$

Based on Eq. (5) and analogous to attenuation-based CT reconstruction, as long as one can measure the phase shift, tomographic reconstruction principles can be applied to the local distribution of electron density. To accomplish this, the phase shift is measured around the image object from many view angles, and the local electron density distribution is then reconstructed using an appropriate image reconstruction algorithm [7, 8]. This is the physical foundation of phase contrast CT.

However, direct measurement of phase shift is often very difficult in practice. Phase shifts need to be connected to other quantities that are easier to measure. The refraction angle, which is the angular deviation of the propagation direction of an exit wave from its incident propagation direction, is a measureable quantity to which phase shift can be directly related. Assuming that the x-ray wave propagates along the z-direction, the refraction phenomenon can be measured in the xy-plane, which is perpendicular to the wave propagation direction. The refraction angle Θ is related to the phase shift as follows [9–11]:

$$\Theta(x, y) = \frac{\lambda}{2\pi} \frac{\partial}{\partial x} \phi(x, y). \quad (7)$$

This relationship has been used as a foundation in modern optics to investigate material properties [4]. However, observation of this refraction effect for diagnostic x-rays is still very difficult as the refraction angle is on the order of micro-radians. In past years, investigators have tried many different schemes to measure the refraction angle or its variants. In the following sections, a review of each method developed by investigators to measure the refraction angles, or more generally, the phase-shift of x-rays when propagating through an image object is given.

Interference method using an additional reference beam

The x-ray interferometry method was pioneered by Bonse and Hart [12]. As schematically shown in Fig. (1), the Bonse-Hart method uses three silicon crystal plates. When the incident x-ray beams satisfy the Bragg diffraction conditions, the incident beam is split into two beams. The two beams are mirrored back towards the analyzer crystal. The image object is placed in the path of one of the beams between the mirror and analyzer crystals. After the beam propagates through the image object, a phase shift is introduced in the beam. This beam then interferes with the other beam to generate modulations in x-ray intensity. In order to determine the relative phase change, a phase shifter can be placed into the reference beam to perform phase stepping. The resulting intensity modulation profile at the detector plane can be written as:

$$I(x, y) = I_0(x, y) + I_1(x, y) \cos[\phi(x, y) + \phi_0], \quad (8)$$

where $\phi(x, y)$ is the local phase shift, ϕ_0 is the baseline phase introduced by the phase shifter, I_0 is the mean signal level, and I_1 is the modulation amplitude. Using a phase 2π

stepping method to change the baseline phase $\phi_0 = j \frac{2\pi}{M}$ ($j=1, 2, \dots, M$) in M steps, one can solve the resulting system of equations to obtain the local phase shift $\phi(x, y)$. The minimal number of phase steps is three ($M=3$), since there are three unknowns in Eq. (8): $I_0(x, y)$, $I_1(x, y)$, $\phi(x, y)$. When more than three phase steps are used, phase-shift can be determined using the first coefficient of the Fourier transform taken with respect to phase steps:

$$\sum_{j=1}^M I_j(x, y) e^{-i \frac{2\pi j}{M}} = \frac{M I_1(x, y)}{2} e^{i \phi(x, y)}. \quad (9)$$

Therefore, the phase-shift is given as:

$$\varphi(x, y) = \arg \left\{ \sum_{j=1}^M I_j(x, y) e^{-i \frac{2\pi j}{M}} \right\}, \quad (10)$$

$$I_j(x, y) = I_0(x, y) + I_1(x, y) \cos \left[\varphi(x, y) + j \frac{2\pi}{M} \right]. \quad (11)$$

More details regarding the phase-step technique are given in the grating interferometer discussion section. The image object is rotated, and the local phase shift is extracted at each object position. This procedure measures a series of line integrals given by Eq. (5). After this step, a tomographic reconstruction is performed to obtain the local distribution of the electron density. A sample image from this type of interferometric system is shown in Fig. (2) [13].

Potential applications of the interference method were investigated [14–16] using synchrotron x-ray facilities, which would be difficult to implement in a clinical setting. The design of the interferometer results in a system which is extremely sensitive, and achieving the required levels of stability can be difficult. Due to this sensitivity, the crystal plates are fabricated from a single piece of silicon, and the resulting field of view is therefore limited to a few centimeters. Combined with the need for a synchrotron, the eventual clinical utility of such a system may prove limited [17].

Diffraction enhanced imaging

A typical setup of a diffraction-enhanced imaging (DEI) system uses synchrotron radiation, silicon crystals, and very sensitive angular filters to produce images of the gradients of the refractive indices of samples. The method was explored by Ingall and Beliaevskaya [18], Davis, et al. [9], Chapman, et al. [19–22], and the medical application of the technology has been pioneered by Pisano and others [20, 21, 23].

The physical principle in diffraction enhanced imaging method is to measure the refraction angle of x-ray beams after passing through an object. As shown schematically in Fig. (3), the key components of the DEI method are the beam monochromator and the beam analyzer, which are made of silicon crystals. In the first stage, the x-ray beam is made nearly monochromatic by selecting an appropriate crystal orientation to satisfy the Bragg diffraction for a specific beam energy. When the nearly monochromatic x-ray beam propagates through the object, phase shifts cause the beam to deviate from the incident propagation direction. The refraction leads to a variation in incident angle on the analyzer crystal. As a result, due to the deviation from the Bragg diffraction condition, the beam intensity changes after it is diffracted by the analyzer crystal.

Suppose the deviation from the Bragg angle θ_B is θ , then the beam intensity after the analyzer crystal at the diffraction angle, $\theta_B + \theta$, is given by

$$I = I_R R(\theta_B + \theta) \quad (12)$$

Here $R(\varphi)$ is profile of the analyzer reflectivity and I_R is the incident beam intensity at the analyzer crystal [5]. This curve is frequently referred to as a rocking curve in the literature. The steepest slope of the rocking curve is located at two angles, $\theta = \pm \theta_D/2$, corresponding to the half maximum of the curve. The full width at the half maximum is called the Darwin width, θ_D .

In DEI, the analyzer is set to $\theta = \pm \theta_D/2$. At this angle, the reflectivity will be 50% if the incident beam does not experience any phase-shift. However, when a phase shift occurs in an object, the beam will refract at an angle Θ . As a result, the diffracted beam intensity becomes [19]:

$$I = I_R R\left(\theta_B \pm \frac{\theta_D}{2} + \Theta\right) \quad (13)$$

By expanding the above expression at the angles $\theta_H = \theta_B + \frac{\theta_D}{2}$ and $\theta_L = \theta_B - \frac{\theta_D}{2}$, one can obtain two equations for the two unknowns I_R and Θ ,

$$I_L = I_R \left[R(\theta_L) + \frac{dR}{d\theta}(\theta_L) \Theta \right] \quad (14)$$

$$I_H = I_R \left[R(\theta_H) + \frac{dR}{d\theta}(\theta_H) \Theta \right], \quad (15)$$

where I_L and I_H are the measured beam intensities at the two analyzer positions. Solving the above equations, one can obtain the refraction angle Θ :

$$\Theta = \frac{I_H R(\theta_L) - I_L R(\theta_H)}{I_L R'(\theta_H) - I_H R'(\theta_L)}, \quad (16)$$

where $R' = dR/d\theta$ is the first order derivative of the rocking curve.

As the image object rotates, one can measure the refraction angles at each object position. Electron density images can then be reconstructed using the basic relationship given by Eqs. (5) and (7) and the corresponding image reconstruction algorithms [24–27].

The DEI method has been explored primarily using synchrotron radiation. However, one can also generate quasi-monochromatic x-ray beams using a conventional x-ray tube and spectral filtering. Most recently, using the heavily filtered x-ray spectrum around the characteristic x-ray K_α peaks, Pisano and Zhong's group constructed a benchtop system using an x-ray tube for preliminary biological imaging tests [28, 29]. An example of an image acquired with this system is shown in Fig. (4) [30]. Thus far the x-ray tube-based method has only been applied to projection imaging. After heavy spectral filtration and passage through the monochromator, the available x-ray flux is limited for near-term use in medical imaging. In addition, the x-ray efficiency in this method is also reduced due to x-ray loss at the analyzer crystal. The use of monochromatic radiation will, however, prove beneficial for lowering radiation dose levels to patients.

As discussed above, the clinical utility of DEI may ultimately be limited by the requirement for highly-monochromatic x-ray beams. Historically, because a synchrotron allows for the use of monochromator while simultaneously retaining a high level of flux, it has been the most widely used source of radiation for this imaging method. The recent results with a conventional x-ray tube and monochromator have brought the technique closer to a clinical setting, though the flux is severely limited. When using a conventional x-ray tube, the technique currently requires imaging times on the order of hours for a single projection using a 1kW x-ray tube. Future improvements in x-ray detector design and increases in tube power may, however, result in substantial reductions in imaging time.

Interferometry-based phase-contrast imaging, diffraction-enhanced imaging, and conventional absorption images of phantoms and breast specimens have been compared [31, 32]. It was found that both phase contrast techniques could provide significantly improved feature detection at a radiation dose that is comparable to or less than the clinical dose.

In-line holography method

Based on the principle developed by Gabor in 1948, in-line phase-contrast radiography, which exploits Fresnel diffraction, was pioneered by Snigirev, et al. [33] and Wilkins, et al. [34]. As shown in Fig. (5), refracted components of a free-propagating wave downstream of the image object interfere, allowing the formation of an interference pattern without additional x-ray optics. This modulated pattern is referred to as a hologram. In conventional holographic imaging with long wavelengths, a reference beam is used to illuminate the hologram to reconstruct the image object. In x-ray in-line holography phase contrast imaging, there is no attempt to conduct the conventional holographic reconstruction step. Instead, the focus is to understand how the phase-shift is encoded into the hologram.

In order to understand the physical principles, the propagation of an x-ray wave field is described by a transmission function [35, 36]:

$$T(x, y) = A(x, y)e^{i\phi(x, y)} = e^{-P_\mu(x, y)/2} e^{i\phi(x, y)}, \quad (17)$$

where the propagation direction of the x-ray wave is assumed to be along the z-direction, $\phi(x, y)$ is the phase shift given in Eq. (5), and P_μ is the line integral of the attenuation coefficient along the z-direction. When a spherical wave propagates through an image object and arrives at the detector plane at a distance z from the source, under the paraxial approximation, the diffracted x-ray wave field is given by [4, 37]:

$$f(x, y; z) = \frac{i}{\lambda z} e^{ikz} \iint dx_0 dy_0 T(x_0, y_0) e^{i\frac{k}{2z}[(x-x_0)^2 + (y-y_0)^2]} \quad (18)$$

where $k = 2\pi/\lambda$ is the wave number. The integral is performed over the surface of the image object. A general analytical calculation of the above Fresnel integral is almost impossible. However, when the image object is assumed to be only weakly perturbing in phase without any absorption, the transmission function can be approximated as:

$$T(x, y) \approx 1 + i\phi(x, y). \quad (19)$$

Under this stringent condition, one can obtain [34],

$$I(x, y, z) \approx 1 - \frac{\lambda z}{2\pi} \nabla^2 \phi(x, y). \quad (20)$$

In other words, the wave front distortion will cause intensity changes that lead to contrast in the hologram. By observing the changes in x-ray intensity, one can observe the potential contrast generated by phase shifts caused by the image object.

The contrast generally forms bright and dark fringes at tissue boundaries. The edge enhancement generated relies on high spatial coherence of the x-ray source, the optimal positioning of detector, and the x-ray energy. Note that the spatial coherence d length

$\ell_c \propto \lambda \frac{d}{f}$, where λ is the wavelength, d is the distance from source to image object, and f is the focal spot size. As a result, for a feasible source to object distance in medical imaging, the focal spot size will have to be decreased to a few microns, which is acceptable for small animal and tissue specimen imaging, but not for larger image objects, due to the extremely limited x-ray flux from a micro-focus x-ray tube.

In addition, although the above simple analysis gives a physical picture as to how phase contrast is generated in in-line holography, the approximation given by Eqs. (19) and (20) will never be satisfied. A more realistic analysis was performed by Wu and Liu and other investigators [35, 38–41]. The results demonstrated a delicate interplay between the absorption and phase contrast in in-line holography. In particular, when an image object is primarily soft tissue, such as breast tissue, a duality between phase shift contribution and absorption contribution can be established [42, 43]. Using the duality, phase retrieval can be achieved from the in-line holograms.

The in-line holography technique has a definite advantage in ease of implementation of the image system. Other than satisfying requirements on source size and object to detector distance, no other specific hardware needs to be added. A limitation of the method is that the measured quantity is the Laplacian of the electron density. This makes accurate reconstruction of electron density very challenging [44]. Thus, in-line holography is often used to enhance edges of an image, which may find use in x-ray phase contrast mammography [34, 41, 45–49]. This method has the distinction of being the only phase contrast imaging technique currently being exploited in clinical practice, where it is marketed as an edge enhancement method for the Konica Minolta RegiusPureView system (Konica Minolta, Tokyo, Japan). The further developments into the duality [42, 43] between the phase and absorption contrast significantly increase the understanding of in-line holography phase contrast imaging. Successful phase retrieval also moves toward tomographic imaging using in-line holography [43, 44, 50, 51].

Coded Aperture method

In recent years, several new methods have been introduced for x-ray phase contrast imaging. One new method uses two apertures to detect small angular deflections due to refraction as intensity changes at the detector [52–55]. A diagram of the system is illustrated in Fig. (7). The beam from the x-ray tube is first divided into many narrow shaped beams by the pre-sample coded aperture. A second coded aperture is located immediately before the detector, aligned with the attenuating portions over the pixel edges. The relative alignment between the two coded apertures is set to allow a portion of each shaped beam to fall on the open pixel area, with the remainder of the beam blocked by the coded aperture placed before the detector. If a sample is now placed in the beam, refraction will cause a deflection of the shaped beams. If the beam is deflected into the open pixel area there will be a relative increase in signal compared to the measurement before the sample was placed in the beam. The opposite will be true if the beam is deflected away from the open pixel area. The magnitude of the signal change will be proportional to the refraction angle, and higher sensitivities will be realized for more narrowly shaped beams.

This method has the advantage of being purely geometrical in nature, and does not depend on the degree of spatial coherence of the incoming x-ray beam. It also does not require phase stepping or other scanning techniques to obtain the measured signal. However, due to the blurring of the shaped beams at the detector and due to the finite source size, initial experiments used a 100 μm focal spot size with a 2m source to detector distance [52]. This focal spot size limitation, combined with the use of two coded apertures, may impose x-ray flux and imaging time limitations if used for clinical applications.

Grating-based interferometer method

A second recently developed phase contrast imaging method uses a Talbot-Lau interferometer. In this method, the measurement of the x-ray refraction angle is converted into the measurement of intensity modulations using a grating interferometer [11, 14, 15, 56, 57]. As shown in Fig. (8), a grating, G_1 , is used to diffract the incident wave into secondary wavelets. In general, the grating can be either an absorption grating or a pure phase grating. In practice, to improve x-ray efficiency, a phase grating with the highest diffraction efficiency is preferred. This makes the pure phase grating with a π -phase shift a natural choice due to its high diffraction efficiency to the diffracted beamlet [4, 37]. When a phase grating with π -phase shift is used, the incident wave is diffracted into the ± 1 primary wavelets and higher order wavelets at each slit [37]. The diffracted primary wavelets from two adjacent grating slits interfere to generate intensity modulations and encode the refraction angle into intensity modulations [37]. For a phase grating with a π -phase shift, the highest contrast of the intensity modulation is observed at the fractional Talbot distance downstream from the grating [11, 57–59]:

$$d = \left(\frac{2m-1}{16} \right) \left(\frac{2p^2}{\lambda} \right) = \frac{2m-1}{16} Z_T, \quad (21)$$

where $Z_T = 2p^2/\lambda$ is the Talbot distance, p is the grating pitch, λ is the x-ray wavelength, and m is fractional Talbot number. The interference pattern has a period of only half of the phase grating pitch. When an image object is placed in the beam, wavefront distortion occurs due to the phase shift caused by the image object. As a result, additional phase given by the refraction angle is introduced into the beam intensity modulations [11, 15]:

$$I(x, y) \cong I_0 + I_1 \cos \left[2\pi \frac{x}{p_2} + \phi_d(x, y) \right] \quad (22)$$

where $p_2 = p/2$ and the signal phase shift ϕ_d is directly related to the refraction angle. Thereby, by analyzing the intensity modulation pattern, one is able to measure the refraction angle, Θ , and reconstruct local electron density using tomographic imaging principles.

Phase stepping method to retrieve refraction angle

To record changes in phase due to the presence of an object, changes in the replicated intensity modulation pattern at the fractional Talbot distance must be analyzed. However, when a detector with a pixel pitch greater than half of the G_1 grating pitch is used to record x-ray intensity changes, the detector will average the intensity of the modulation pattern. This will be the case with nearly all detectors, which typically have pixel pitches greater than 50 μm compared with the G_1 pitch of 2–4 μm . This averaging of the sinusoidally modulating intensity signal will result in a loss of the encoded information. To avoid this pixel-level averaging, an absorption grating, G_2 , with the same pitch as the intensity modulation, is placed directly before the detector. The G_2 grating is translated by a fraction of the detector pitch, and the average intensity at each detector element is recorded for each

G_2 position. This procedure is illustrated in Fig. (9). At each detector pixel, (m,n) , the image intensity changes as a function of the G_2 position, x_g , as follows [11, 15, 57]:

$$I(m, n; x_g) \cong I_0(m, n) + I_1(m, n) \cos \left[2\pi \frac{x_g}{p_2} + \phi_d(m, n) \right], \quad x_g = jD/N. \quad (23)$$

Here D is the detector pitch and N is the total number of phase steps. Similar to the method described in Eqs. (9)–(11), after recording x-ray intensity at a given detector pixel for several phase steps, one can take a Fourier transform with respect to the variable x_g to obtain the refraction angle at the detector pixel (m,n) . The ϕ_d term in Eq. (23) is measured with and without the object, and the phase shift between the two measurements gives the differential phase due to the presence of the object.

The mean intensity over the phase steps is the DC component of Eq. (23), which is the conventional absorption intensity. Thus, a data acquisition process for refraction angle gives attenuation intensity as well. A sample image is given in Fig. (10) to demonstrate the differential phase contrast image and the absorption image of a plastic rod using an experimental grating interferometer system at the University of Wisconsin-Madison. The figure clearly demonstrates the differential nature of the phase contrast projection.

Spatial coherence requirement and the role of the source grating

In order to enable interference downstream of the phase grating, the incident wave at the phase grating position must be spatially coherent. The minimal requirement is that the spatial coherence length, ℓ_c , should be of the order of the pitch of the phase grating, $\ell_c \sim p_1$. Using classical coherence theory [4], the spatial coherence of a source with size, s ,

wavelength, λ , and distance, d_1 , is given by $\ell_c \propto \lambda \frac{d_1}{s}$. Thus, when a diagnostic x-ray tube is used, with focal spot size of approximately 1.0 mm, the coherence length is too short to enable phase contrast imaging.

A method developed by Pfeiffer, et al. [60] accounts for the large focal spot size of a standard diagnostic x-ray tube. Another absorption grating (G_0 grating in Fig. 8) with openings of 10–50 μm is used to split the x-ray beam into many parallel beamlets. For each beamlet, the spatial coherence is determined by the grating opening, not by the focal spot size. The additional complexity in fabrication is justified because the use of many parallel beamlets allows for better use of available x-ray flux relative to a single slit.

Fig. (11) shows a reconstructed image of a breast tissue sample imaged with an experimental grating interferometer system at the University of Wisconsin-Madison. The particular sample contained a highly malignant carcinoma, and the additional contrast gained from phase sensitive imaging is clearly visible.

For quantitative imaging of larger objects, the clinical utility of grating-based x-ray interferometry is perhaps the most promising among the other phase sensitive imaging methods reviewed thus far. Unlike many of the other methods, the requirement of monochromatic, highly-spatially window. coherent x-ray sources can be significantly relaxed, resulting in a significant increase in the available x-rays that can be used for imaging from a standard x-ray tube. In addition, the resulting images maintain high spatial resolution, allowing for images which are comparable to the best x-ray attenuation based systems. A limiting factor of such a system could certainly be the fabrication of the x-ray gratings, although once the optimal technique has been determined, this would no longer be an issue. This technique simultaneously acquires several types of images, each with a

different x-ray contrast mechanism. Such an acquisition allows for more quantitative imaging, with separate maps of electron density and effective atomic number, which were previously inseparable from a standard, single energy x-ray image.

Concluding Remarks

A variety of methods have been introduced to implement x-ray phase sensitive imaging and the corresponding computed tomographic reconstruction of the local distribution of electron density. Preclinical studies have been conducted by several groups to demonstrate clinical potentials for each method. For phase contrast projection imaging, the measurement of the refraction angle corresponds to the line integral of the first- or higher-order derivative of the local electron density distribution. As a result, phase contrast imaging often provides images with enhanced edges at the boundaries within an object. This enhancement may provide better delineation of lesions in clinical practice. When the corresponding tomographic reconstruction is performed, the electron density can be measured quantitatively. This quantification has the potential to provide accurate classification of tissue types, in particular, the ability to delineate diseased from healthy tissue.

Currently, the majority of investigations are still limited to the use of synchrotron radiation. The experimental results from the synchrotron facilities provide very important insights into two aspects. The first is an understanding of x-ray phase contrast signatures of specific diseased tissues for use in medical diagnosis. The second is the use of nearly ideal coherent x-ray beams to determine relevant physical parameters for future medical devices which would use conventional x-ray tubes.

However, to make x-ray phase sensitive imaging practical in routine medical practice, the following issues must be addressed:

1. **X-ray source requirement:** Independent of the contrast mechanism used in imaging, x-ray photons must be sufficiently energetic to be able to penetrate through the image object. In preclinical applications, such as tissue specimen imaging, photon energies can be as low as 10keV for acceptable signal level at the detector plane. However, when a more attenuating object is imaged, such as an entire organ or portion of the human body, the low energy photons will be entirely absorbed. Therefore, it is important to extend the preclinical experimental conditions to higher energy x-ray photons. Ideally, the mean x-ray energy should be on the order of 50keV for most human clinical applications. In addition to photon energy, it is also important that there is sufficient photon flux in order to achieve the required signal to noise ratio (SNR) at the detector. Therefore, near-future studies will have to focus on demonstrating the feasibility of phase sensitive x-ray imaging using a conventional diagnostic x-ray tube and realistically-sized image objects to further demonstrate the clinical relevance of each proposed phase sensitive imaging method.
2. **X-ray detector requirement:** Different phase sensitive imaging methods may have different requirements for detector resolution. In particular, for the coded aperture and in-line holographic methods, the detector resolution has a direct impact on the sensitivity of the method. For all methods, the detective quantum efficiency of the detector always needs to be sufficient to match the signal level in a specific clinical application. Therefore, there is a clear need to determine whether the detector performance is a limiting factor in the efficiency for a specific phase sensitive imaging method.
3. **X-ray radiation dose:** Currently, for physical phantom or tissue specimen experiments, x-ray radiation dose is not a major concern. One can always increase

the x-ray exposure level to increase the SNR. However, in clinical applications, the feasibility of achieving acceptable SNR at a clinically-acceptable radiation dose level needs to be demonstrated.

4. Data acquisition time consideration: Currently, due to limited x-ray source capacity when using conventional x-ray tube sources, the data acquisition time has been prolonged significantly to boost the SNR. While this may be acceptable in preclinical experiments, for routine clinical applications, data acquisition must take seconds, not hours as used in the current laboratory work. In order to address this issue, aside from a more powerful x-ray source and improved detector, it is also important to explore innovative data acquisition and corresponding imaging processing methods to reduce data acquisition time. When other accessory devices are used, such as x-ray gratings or coded apertures, it is important to optimize the efficiency of these devices to improve overall efficiency and thus reduce data acquisition time.
5. Robustness of the imaging method: when x-ray phase sensitive imaging is used, it often involves a different requirement on the spatial coherence of the x-ray beams compared with standard x-ray imaging. When a spatially coherent x-ray wave is scattered by a granular structure inside the image object, the coherence will be diminished. As a result, the SNR of the phase contrast mechanism drops, and may even be completely lost. This is in stark contrast with the absorption contrast mechanism which is much more independent of the structure of the image object. Therefore, the phase contrast mechanism should perhaps be combined with conventional absorption contrast for medical diagnosis. Instead of using phase contrast as the sole contrast mechanism in medical diagnosis, a potential new paradigm in the future of x-ray imaging could be multi-contrast imaging, where the complementary information from each contrast mechanism is combined for use in medical diagnosis.

In conclusion, x-ray phase sensitive imaging is an exciting and potentially important method in medical applications. However, significantly more research is required before it will reach its full potential for use in clinical applications.

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Fig. 1.

An x-ray interferometer setup. Three crystal plates, the splitter, mirror, and analyzer, operate as the components of an x-ray interferometer. The system generates interference fringes produced by phase changes in one of the beams as it passes through the object.

Fig. 2.

(a) Phase-contrast X-ray CT image of normal rat liver. (b) Phase-contrast X-ray CT image of VX-2 cancer lesion of rabbit's liver. Scale bar: 1 mm [13].

Fig. 3.

A diffraction-enhanced imaging setup. An x-ray beam passes through a monochromator, then the object, and finally is analyzed by the angular filter before being incident on the detector. Variation in the refraction through the object causes changes in the relative angle on the analyzer, changing the reflection and contrast produced.

Fig. 4. Full-thickness breast specimen image acquired using a GE Senographe 2000D (GE, Paris, France) (a) conventional digital mammographic system and (b) a corresponding image acquired using the compact diffraction-enhanced imaging system [30].

Fig. 5.

An in-line holography illustration. A wave-front passes through an object which distorts the wave-front. The detector is placed behind the object, at a sufficient distance d , to allow interference fringes to form without additional x-ray imaging optics.

Fig. 6.

(a) Attenuation and (b) phase contrast image of lumpectomy specimen. Both images were acquired at 40kVp with the same entrance exposure. The images were acquired using prototype systems developed at the University of Oklahoma (Dr. Hong Liu), in collaborations with University of Alabama at Birmingham (Dr. Xizeng Wu) and University of Iowa (Dr. Laurie Fajardo). [Courtesy: Dr. Hong Liu, University of Oklahoma]

Fig. 7.

Coded Aperture imaging system illustration. An incoming beam, from an x-ray tube in this illustration, is incident on a coded aperture, which attenuates a portion of the beam, creating many narrow shaped beams. A portion of the beams proceed through the object, which refracts them on their path to the detector. The addition of a second coded aperture before the detector allows the deflections of the beams to be recorded as intensity changes.

Fig. 8.

Illustration of the Talbot-Lau grating based interferometer system. An incoherent x-ray source provided by a standard x-ray tube is placed behind the source grating, G_0 , which cuts the beam into a series of vertical beamlets, increasing the spatial coherence of the beam. The beam passes through the image object and then the phase grating, G_1 , which introduces a relative π -phase shift into beam at a 50% duty cycle. This causes a replication of the grating pattern at fractional Talbot distances. The final analyzer grating, G_2 , is placed at a fractional Talbot distance.

Fig. 9.

Illustration of the phase-stepping method for extraction of the differential phase contrast signal from the measured projection data. Each letter represents one step position of the analyzer grating. The electric field intensity at the face of the grating is a replication of the phase grating pattern and is in the same position for each of the phase steps of a given view. The total contribution of the field which is transmitted through the grating is summed by each pixel. The intensity at each pixel is recorded at each step position and the phase of the pixel intensity modulation is compared between when the object is present compared to when it is not.

Fig. 10.

Differential phase and absorption projection images of a plastic rod. The left column contains a differential phase contrast projection (top left), a line profile through the rod (bottom left). The differential line profile shows the nature of the differential projection image, where only regions of sudden change will contain contrast, e.g. the edges of a rod. The right column shows a typical attenuation image (top right) and line profile (bottom right), where the largest signal comes from the most attenuating part of the image, the center.

Fig. 11.

Reconstructed (a) phase contrast and (b) conventional attenuation images of a breast tissue sample containing a highly malignant carcinoma. The phase contrast image shows significant contrast between the central tissue portion and water near the outer wall of the cylinder (indicated by arrow). The absorption image shows little to no contrast in this region, even in a narrow viewing