Review paper

X-ray phase imaging reaching clinical uses

Atsushi Momose

Institute of Multidisciplinary Research for Advanced Materials, Tohoku University, 2-1-1 Katahira, Aoba-ku, Sendai 980-8577, Japan

ARTICLE INFO

Keywords:

Phase contrast
Refraction
Interference
Scattering
Grating
Mammography
Arthritis
Chronic obstructive pulmonary disease

ABSTRACT

X-ray phase imaging that uses the phenomena of X-ray refraction and scattering to generate image contrast has the potential to overcome the drawback of conventional X-ray radiography in observing biological soft tissues. After its dawn at synchrotron radiation facilities 30 years ago, the development of X-ray phase imaging is expanding to hospitals by grating-based phase-imaging approaches available with a conventional X-ray tube. In this review, after introducing the physical advantages and methodological details of X-ray phase imaging, recent trials of instrumentation in hospitals for diagnoses of rheumatoid arthritis and chronic obstructive pulmonary disease are introduced.

1. Introduction

The sensational discovery of the X-ray in 1895 by W. C. Röntgen [1] dramatically changed medical diagnosis at that time by visualizing the inside of living bodies. Although it took some time before the real nature of the X-ray was elucidated, it was considered that unknown rays penetrated straight through objects (e.g., hands), and a transmission image depicting inner structures (e.g., bones) was observed on a scintillator screen. Nowadays, X-ray absorption coefficients are used to describe the contrast in the transmission image. Materials containing atoms of higher atomic numbers at higher densities have higher absorption coefficients. Therefore, bones are differentiated from soft tissues.

The fact that an X-ray is an electro-magnetic wave with a wavelength comparable to the size of the atom was confirmed by the discovery of X-ray diffraction by von Laue [2] in 1912. The diffraction phenomenon by crystals was explained as interference of X-ray waves whose wavelength is shorter than the distances between atoms. Following this understanding, X-ray crystallography was initiated. However, in X-ray radiography, the wave nature of X-rays was not utilized, and the contrast mechanism in transmission imaging has been based on the X-ray attenuation (i.e., absorption contrast) up to now. Since the absorption coefficient is remarkably lower for lighter elements, such as H, C, O, N, etc., X-ray contrast generated by biological soft tissues or polymers is not clear. This fact has been considered a drawback of X-ray radiography for a long time. Although the use of contrast agents containing heavy elements is an approach for overcoming this drawback, its availability is

limited and side effects by contrast agents are occasionally problematic in medicine.

In the history of optical microscopy, there was a brilliant achievement or innovation which enabled the depiction of transparent objects by using phase contrast [3]. The wave nature of light causing interference effects was utilized to develop various phase-contrast optical microscopes for transparent biological samples.

The same situation exists in the region of X-rays. By exploring phase-contrast X-ray imaging methods, the internal structures in biological soft tissues and polymers can be depicted even if absorption contrast is not clear. However, generating X-ray phase contrast is not as easy as generating visible light phase contrast. This is because of the fact that the refractive indices of any materials in the X-ray region are close to unity. Therefore, it is not easy to realize X-ray optical elements, such as mirrors and lenses, and constructing X-ray phase-contrast apparatus is not straightforward. Another obstacle in developing X-ray phase-contrast methods is the fact that the spatial coherency of X-rays must be ensured to some extent to cause interference phenomena. Conventional X-ray tubes do not meet this demand.

Nevertheless, in the 1990s (about one century after the discovery of X-rays), several techniques for X-ray phase-contrast generation were proposed and demonstrated [4–7]. Their developments were mainly undertaken at synchrotron radiation facilities based on huge accelerator systems to provide collimated and high-intensity X-ray beams. The high quality of the X-ray beams were convenient for causing interference effects for phase-contrast generation.

The development of digital X-ray image detectors in that decade

E-mail address: atsushi.momose.c2@tohoku.ac.jp.

<https://doi.org/10.1016/j.ejmp.2020.11.003>

Received 31 August 2020; Received in revised form 20 October 2020; Accepted 1 November 2020

Available online 17 November 2020

1120-1797/© 2020 Associazione Italiana di Fisica Medica. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

played another important role. Beyond recording and observing phase-contrast images simply on X-ray films, relevant physical quantities (absorption, phase shift or differential phase shift, and scattering), the effects of which co-exist in phase-contrast images, were extracted separately through digital processing. Quantitative images mapping those quantities were generated through computer calculation from phase-contrast images acquired in specific manners. In this review, the term ‘phase imaging’ is used to describe this procedure inclusive of the acquisition of phase-contrast images. This quantitative process is therefore compatible with X-ray computed tomography (X-ray CT) [8] that reconstructs sectional images without cutting objects, allowing the depiction of internal structures of objects three dimensionally.

Synchrotron radiation is useful for pre-clinical study of X-ray phase imaging because the potential of X-ray phase imaging in depicting biological soft tissue structures can be precisely examined by observing specimens. After pre-clinical study, clinical use of X-ray phase imaging should be the eventual target by applying it to patients (that is, living bodies), and a clinical system with synchrotron radiation is under study [9]. However, X-ray phase imaging performed at synchrotron radiation facilities is not convenient because the location and opportunity are quite limited for use, and therefore X-ray phase imaging available at hospitals is strongly expected.

The X-ray phase-imaging techniques developed at synchrotron radiation facilities were not translated as they are to the systems employing an X-ray tube because of the limited X-ray flux available for phase-contrast generation. Meanwhile, the X-ray grating interferometry [10,11] appearing in the 2000s brought the opportunity of X-ray phase imaging in hospitals with conventional X-ray tubes. Recently, systems for the diagnoses of rheumatoid arthritis [12] and chronic obstructive pulmonary disease [13] have been built and operated in hospitals. In this review, especially from a physical point of view, after describing the potential and principle of X-ray phase imaging, the developments of grating-based X-ray phase imaging towards clinical systems are reviewed with future prospects.

2. What is X-ray phase imaging?

2.1. Significance of using X-ray phase information

A wave is characterized by wavelength, amplitude, and phase. In X-ray phase imaging, we consider elastic interaction that does not cause the change in the wavelength. When a wave of X-rays penetrates through an object, its amplitude is reduced and its phase is shifted. While the amplitude reduction corresponds to X-ray attenuation, the phase shift is the signal of X-ray phase imaging. To describe these quantities, we can use complex refractive index $n (=1 - \delta + i\beta)$, where imaginary part β describes the X-ray attenuation and the phase shift is given by δ . Both δ and β are small quantities in the hard X-ray region, reflecting the fact that X-rays penetrate inside objects nearly straight. What is important here is another fact that the ratio δ/β is around 1,000 for materials consisting of light elements, such as polymers and biological soft tissues.

Let us consider a uniform object of thickness T . X-ray attenuation follows Lambert-Beer's law, and optical density D :

$$D = -\log\left(\frac{I}{I_0}\right) = \mu T \quad (1)$$

is measured in conventional X-ray radiography, where I_0 and I are the X-ray intensities in front of and behind the object and μ is the linear absorption coefficient. Strictly speaking, the linear absorption coefficient is a function of position $\mu(x, y, z)$ and Eq. (1) is rewritten as

$$D(x, y) = \int \mu(x, y, z) dz, \quad (2)$$

where it is assumed that X-rays penetrate in the z direction. By using β

and X-ray wavelength λ ,

$$D(x, y) = \frac{4\pi}{\lambda} \int \beta(x, y, z) dz. \quad (3)$$

Phase shift Φ also occurs in proportion to the thickness for uniform objects. In the case of a non-uniform object placed in air (i.e., $n = 1$), phase shift $\Phi(x, y)$ is given by

$$\Phi(x, y) = \frac{2\pi}{\lambda} \int \delta(x, y, z) dz. \quad (4)$$

δ and β are described by using atomic quantities as follows:

$$\delta = \frac{r_e \lambda^2}{2\pi} \sum_k N_k (Z_k + f'_k) \equiv \frac{\lambda}{2\pi} \sum_k N_k p_k, \quad (5)$$

$$\beta = \frac{\lambda}{4\pi} \sum_k N_k \mu_k^a, \quad (6)$$

where N_k , Z_k , f'_k , and μ_k^a are the atomic density, atomic number, real part of the atomic scattering factor, and the atomic absorption coefficient of element k existing in the object. μ_k^a has the dimension of area and corresponds to the interaction cross section. Note that the interactions relating to X-ray attenuation are the photoelectron effect, Thomson scattering, and Compton scattering, and μ_k^a is the quantity defined by summing the effects of the three interactions. In Eq. (5), p_k ($\equiv r_e \lambda (Z_k + f'_k)$) is used as the interaction cross section of the phase shift [14]. The difference between D and Φ is derived from the difference between μ_k^a and p_k . Note that the constitution and density affects both D and Φ in the same manner.

Fig. 1 shows plots of μ_k^a and p_k for X-ray photon energies of 20 keV, 40 keV, and 60 keV as functions of the atomic number. The magnitudes of p_k are larger than those of μ_k^a by about 1,000 times for low-Z elements. This fact suggests that the use of X-ray phase information (phase contrast) has the potential to overcome the drawback of the poor sensitivity of conventional X-ray radiography based on the absorption contrast especially for materials consisting of low-Z elements. Table 1 lists the values of δ and β calculated for some materials at 30 keV and 60 keV photon energies [15]. Ratio δ/β exceeds 1,000 for low-Z materials, inheriting the difference shown in Fig. 1.

Phase shift $\Phi(x, y)$ is equivalent to the change in the form of the wavefront. Considering the fact that a wave propagates in the direction perpendicular to its wavefront, the slope of the wavefront induced by the phase shift implies a change in propagation direction $\varphi(x, y)$ (i.e., ‘refraction’), which is given by

Fig. 1. Interaction cross sections of the phase shift (p_k) and absorption (μ_k^a) per atom, which are used in Eqs. (5) and (6), as a function of atomic number Z . Plots for 20 keV, 40 keV, and 60 keV X-rays are shown.

Table 1

Refractive indices ($1 - \delta + i\beta$) of some materials at 30 keV and 60 keV photon energies.

Material	30 keV			60 keV		
	δ	β	δ/β	δ	β	δ/β
Water	2.56×10^{-7}	1.06×10^{-10}	2.41×10^3	6.42×10^{-8}	2.93×10^{-11}	2.19×10^3
Polyimide	3.38×10^{-7}	1.15×10^{-10}	2.34×10^3	9.70×10^{-8}	5.01×10^{-11}	1.94×10^3
Polypropylene	2.37×10^{-7}	7.01×10^{-11}	3.38×10^3	5.95×10^{-8}	2.39×10^{-11}	2.48×10^3
Teflon	4.87×10^{-7}	2.46×10^{-10}	1.98×10^3	1.22×10^{-7}	7.09×10^{-11}	1.72×10^3
Ti	9.68×10^{-7}	7.08×10^{-9}	1.37×10^2	2.41×10^{-7}	5.60×10^{-10}	4.30×10^2
Fe	1.70×10^{-6}	2.01×10^{-8}	8.46×10^1	4.22×10^{-7}	1.54×10^{-9}	2.74×10^2

$$\varphi(x, y) = \frac{\lambda}{2\pi} \nabla_{\perp} \Phi(x, y) = \int \nabla_{\perp} \delta(x, y, z) dz, \quad (7)$$

where $\nabla_{\perp}$ is the gradient operator in the x - y plane. The value of φ , which strictly depends on the shape of the object, is in the order of micro-radians or less. In conventional X-ray radiography, therefore, it is reasonably assumed that X-rays penetrate straight in objects. In X-ray phase-contrast techniques, however, this slight change in propagation direction is used as a signal.

2.2. X-ray phase-imaging techniques

Since the effect of phase shift or refraction does not appear clearly in conventional X-ray radiography, some optical devices are needed to generate phase contrast. However, as the refractive index in the X-ray region is close to unity, X-ray optical elements, such as mirrors and lenses, are only available under limited conditions, causing difficulty in constructing X-ray phase-contrast optics. Furthermore, a highly collimated X-ray beam (in other words, parallel wave or spherical wave) is necessary to visualize the effect of refraction, avoiding ‘penumbra’. In other words, (partial) spatial coherence is needed. Normal X-ray tubes cannot provide such X-rays with a flux sufficient for imaging.

Nevertheless, in the 1990s, several techniques were proposed and demonstrated mainly by using synchrotron radiation. Fig. 2 illustrates the setups of X-ray phase-contrast techniques studied especially for biomedical purposes.

2.2.1. Method using two-beam interference

The approach for directly measuring phase shift is two-beam interferometry; a beam transmitted through an object (object beam) is combined with a coherent reference beam and interference fringes corresponding to the contours of the phase shift are recorded (Fig. 2(a)). For X-rays that have atomic-scale wavelengths, it is extremely difficult to construct such an interferometer. Unless the optical path difference between the object and the reference beams is kept stable during measurement within a deviation much smaller than the wavelength, interference fringes are smeared out. Nevertheless, Bonse and Hart [16] realized an X-ray interferometer by monolithically cutting out the entire body of an X-ray interferometer from a Si single-crystal ingot. Three crystal lamellae with the same intervals were formed, and incident X-rays to the first lamella (S) were separated into two beams by Bragg diffraction. The two beams reached the second lamella (M) and were similarly diffracted. Two beams among the four beams from M overlap and were diffracted at the third lamella (A), and as a result two interfering beams were generated behind A. By placing an object on one of the interfering beam paths, interference fringes corresponding to the contours of the phase shift were observed.

Interference pattern $I(x, y)$ observed by this interferometer is written as

Fig. 2. Phase-contrast methods studied in the hard X-ray region especially for biomedical and medical purposes: (a) Method using two-beam interference, (b) method using crystal diffraction enhancement, (c) propagation-based method, and (d) grating-based method. A typical phase-contrast image is given at the right of each setup illustration.

$$I(x, y) = A(x, y) + B(x, y) \cos[\Phi(x, y) + \Delta(x, y)], \quad (8)$$

where $A(x, y)$ and $B(x, y)$ are the average intensity and fringe amplitude, respectively. It is not technically easy to fabricate an ideal interferometer without deformation and a built-in moiré pattern is normally observed, as shown in the image of a polymer sphere (Fig. 2(a)), even in the absence of an object. Such an effect is expressed by $\Delta(x, y)$ in Eq. (8).

As mentioned, recoding $I(x, y)$ is not sufficient in performing X-ray phase imaging. Objects normally cause both attenuation and phase shift. The former appears in $A(x, y)$, and it is not easy to extract the effect of the latter ($\Phi(x, y)$) purely. Here, two approaches for differentiating between attenuation and phase shift are explained, that is, the fringe-scanning method [17] (or phase-stepping technique) and the Fourier transform method [18].

2.2.1.1. Fringe-scanning method. This method introduces a tunable phase difference between the object and the reference beams. Interference patterns are written as

$$I_k(x, y) = A(x, y) + B(x, y) \cos \left[\Phi(x, y) + \Delta(x, y) + 2\pi \frac{k}{M} \right], \quad k = 1, 2, \dots, M, \quad (9)$$

where the stepwise change in the phase difference is denoted by k , and M is an integer equal to or larger than 3. Then, by acquiring multiple interference patterns described by Eq. (9), $\Phi(x, y)$ can be extracted by

$$\Phi(x, y) + \Delta(x, y) = \arg \left[\sum_{k=1}^M I_k(x, y) \exp \left(-2\pi i \frac{k}{M} \right) \right], \quad (10)$$

where $\arg[\]$ implies the extraction of the argument. Note that $\Delta(x, y)$ can be determined without an object (that is, $\Phi(x, y) = 0$) using the same procedure. Thanks to this phase-imaging procedure, we can avoid the difficulty of preparing a perfect interferometer. On the other hand, an absorption image is obtained by averaging $I_k(x, y)$ ($k = 1, 2, \dots, M$).

Under the setup of Fig. 2(a), the phase difference can be applied by placing, for instance, a thin glass plate in the reference beam. By inclining it, the effective thickness can be tuned so that Eq. (9) is satisfied [19].

2.2.1.2. Fourier-transform method. This method introduces fine interference fringes (carrier fringes). Assuming that the carrier fringes of spatial frequency f_0 are generated in the x direction, the interference pattern is written as

$$I(x, y) = A(x, y) + B(x, y) \cos[\Phi(x, y) + \Delta(x, y) + 2\pi f_0 x] \quad (11)$$

Further transformation of Eq. (11) yields

$$I(x, y) = A(x, y) + C(x, y) \exp(2\pi i f_0 x) + C^*(x, y) \exp(-2\pi i f_0 x), \quad (11)'$$

where

$$C(x, y) \equiv \frac{1}{2} B(x, y) \exp[i\{\Phi(x, y) + \Delta(x, y)\}], \quad (12)$$

and the asterisk denotes the complex conjugate. The one-dimensional Fourier transform of Eq. (11)' yields

$$I_F(f, y) = A_F(f, y) + C_F(f - f_0, y) + C_F^*(f + f_0, y), \quad (13)$$

where subscript F indicates the Fourier transform of each term in Eq. (11)'. The three terms on the right-hand side of Eq. (13) are separated by f_0 from each other along frequency axis f . If the sizes of the structures involved in the object are sufficiently larger than $1/f_0$, the overlap of the three terms on the f axis is ignored, and $C_F(f - f_0, y)$ can be extracted. Next, $C_F(f, y)$ is obtained by shifting $C_F(f - f_0, y)$ by f_0 to the origin. The inverse Fourier transform of $C_F(f, y)$ with respect to f yields $C(x, y)$. Then, $\Phi(x, y) + \Delta(x, y)$ is obtained by calculating the argument of $C(x, y)$. The determination of $\Delta(x, y)$ is feasible without an object. An absorption image is obtained by the inverse Fourier transform of $A_F(f, y)$.

Under the setup of Fig. 2(a), carrier fringes can be introduced, for instance, by placing a wedge phase plate in the reference beam [14]. This method requires a single interference pattern and is compatible with the purpose of quick imaging unlike the fringe-scanning method described in Section 2.2.2.1. On the other hand, the spatial resolution attained in resultant phase image $\Phi(x, y)$ is limited by $1/f_0$ while the fringe-scanning method can provide phase images with much better spatial resolutions without degradation from interference patterns. Depending on the purpose of phase imaging, we need to select one of the two approaches.

The sensitivity to the phase shift (in other words, detectable smallest phase shift $\Delta\Phi$) is affected by the photon statistics. Apart from other noise sources, such as electric detector noise, $\Delta\Phi \sim 1/\sqrt{N}$ is common for the both approaches, where N is the total number of X-ray photons measured in a detector pixel.

Finally, an obstacle in the phase imaging by two-beam interferometry is pointed out. When the phase shift exceeds 2π , the above-mentioned calculation of the argument, which is $\tan^{-1}$ in practice, does not provide the phase shift directly but the phase shift wrapped within $(-\pi, \pi)$. Therefore, a phase-unwrapping procedure [20] is additionally needed. When too-fine interference fringes are generated in observing an object that causes steep phase shifts, we meet a difficulty in this process. In practice, a sample is immersed, for instance, in water bath for observation because the refraction at the sample surface (sample-air

boundary) is moderated so that the generation of too-fine interference fringes is avoided [19].

2.2.2. Method using crystal diffraction enhancement

Fig. 2(b) shows another approach for generating phase contrast with crystals. Bragg diffraction by a perfect crystal occurs within an angular range of several microradians or smaller. The magnitude of this value is comparable to the angular change induced by X-ray refraction. Therefore, by recording X-rays transmitted through an object via Bragg diffraction by the analyser crystal placed behind the object, a kind of phase contrast is generated because the incident angle to the crystal differs depending on the refraction angle and the diffracted intensity varies [21–23].

The X-ray reflectivity on a perfect crystal is described by a rocking curve $R(\theta - \theta_B)$, which is given by dynamical diffraction theory [24]. When incident angle θ equals Bragg diffraction angle θ_B , the reflectivity reaches its maximum and decreases rapidly with increasing $|\theta - \theta_B|$. When an object is placed in front of the crystal, $I_D(x, y; \theta - \theta_B) \equiv I(x, y) \cdot R(\theta - \theta_B - \varphi_x(x, y))$ is measured, where $I(x, y)$ is the X-ray intensity just behind the object and $\varphi_x(x, y)$ is the x component of $\frac{\lambda}{2\pi} \nabla \perp \Phi(x, y)$ (see Eq. (7)). Here, it is assumed that X-ray diffraction occurs in the plane parallel to the x axis and perpendicular to the y axis.

When multiple images are acquired by rotating the crystal at step-wise angular positions θ_m across the Bragg diffraction condition, $\varphi_x(x, y)$ can be determined by

$$\varphi_x(x, y) = \frac{\sum_m \theta_m I_D(x, y; \theta_m)}{\sum_m I_D(x, y; \theta_m)}. \quad (14)$$

An absorption image can be obtained by averaging $I_D(x, y; \theta_m)$, provided that the angular scan is performed in a fully wide range. More simply, when two images $I_L(x, y)$ and $I_H(x, y)$ are measured at angular positions θ_L and θ_H at the slopes on the low-angle and high-angle sides of the profile of R , $\varphi_x(x, y)$ can be determined approximately by [23]

$$\varphi_x(x, y) = \frac{I_H R(\theta_L) - I_L R(\theta_H)}{I_L \left. \frac{dR}{d\theta} \right|_{\theta=\theta_H} - I_H \left. \frac{dR}{d\theta} \right|_{\theta=\theta_L}}. \quad (15)$$

An absorption image is derived from

$$\left(I_L \left. \frac{dR}{d\theta} \right|_{\theta=\theta_H} - I_H \left. \frac{dR}{d\theta} \right|_{\theta=\theta_L} \right) / \left(R(\theta_L) \left. \frac{dR}{d\theta} \right|_{\theta=\theta_H} - R(\theta_H) \left. \frac{dR}{d\theta} \right|_{\theta=\theta_L} \right) \quad (16)$$

2.2.3. Propagation-based method

If X-rays of sufficient spatial coherency (in other words, X-rays of a well-ordered wavefront) are available, without using any optical devices, another kind of phase contrast is generated by making a certain distance between an object and an image detector, as shown in Fig. 2(c). In conventional X-ray radiography, an object and an image detector are placed as close as possible to avoid image blurring. In this method, the phenomenon of Fresnel diffraction observed with the spatially coherent illumination is utilized [25,26]. Fresnel diffraction appears by the interference between a wave strongly deflected by structural boundaries in an object and a neighboring non-deflected wave. Therefore, a contrast outlining the structural boundaries is observed. In X-ray imaging with synchrotron radiation, this phenomenon occurs routinely, as shown in Fig. 2(c). In the laboratory, microfocus X-ray tubes are used for this purpose. Conventional X-ray tubes with a large focus cause penumbra and the effect of Fresnel diffraction is blurred out and not perceived.

To retrieve the phase information, a recursive approach using multiple images recorded by changing the distance from an object has been developed [27]. Another approach based on the transport-of-intensity equation (TIE) [28] has also been studied [29]. The usage of the TIE is simplified under the assumption of an object consisting of materials having a constant δ/β . Then, the TIE has the form:

$$\nabla_{\perp} \cdot (I(x, y, z) \nabla_{\perp} \Phi(x, y, z)) = -\frac{2\pi}{\lambda} \frac{\partial}{\partial z} I(x, y, z), \quad (17)$$

and, with a single-distance measurement, the phase shift just behind an object can be calculated approximately by

$$\Phi(x, y, z=0) = \frac{\delta}{2\beta} \ln \left[\mathcal{F}^{-1} \left\{ \frac{\mathcal{F}[I(x, y, z)/I_0(x, y, z)]}{1 + z\delta\mu^{-1}(u^2 + v^2)} \right\} \right], \quad (18)$$

where $\mathcal{F}$ and $\mathcal{F}^{-1}$ denote the forward and backward Fourier transforms and u and v are the Fourier conjugate coordinates of x and y , respectively [30].

2.2.4. Grating-based method

Finally, a comparatively new approach with transmission gratings is shown in Fig. 2(d). This method utilizes the striped pattern field produced by the grating (G1) placed in front of (or behind) an object. The striped pattern is normally generated by the (fractional) Talbot effect (or self-imaging effect) [31–33] by the grating with a period of several microns. The positions of the high-contrast striped pattern (so-called ‘self-image’) are given by the self-imaging condition as a function of the grating period, grating type, X-ray wavelength, and source-G1 distance.

The X-ray refraction caused by the object deforms the striped pattern downstream in proportion to the distance from G1 (or the sample) to an X-ray image detector. If an image detector with sufficient spatial resolution is available, the deformed striped pattern can be recorded directly and the structure of the object can be decoded [34]. Even if the striped pattern is not resolved, another grating (G2), whose period is comparable to that of the self-image, is placed (see Fig. 2(d) and Fig. 3(a)), and a moiré pattern is recorded by the normal image detector placed behind G2 [10]. The deformation of the striped pattern is reflected on the moiré pattern. This configuration is known as a Talbot interferometer. A phase grating is normally used for G1, and G2 must be an amplitude grating.

Moiré pattern $I^G(x, y)$ measured by an X-ray Talbot interferometer, for which it is assumed that linear gratings in the y direction are employed, is given by

$$I^G(x, y) = B_0^G(x, y) + \sum_{n>0} B_n^G(x, y) \cos \left[\frac{2\pi n}{d} \{ z\varphi_x(x, y) + \chi + \Delta(x, y) \} \right], \quad (19)$$

where $B_n^G(x, y)$ are calculated from the products of the Fourier coefficients of the self-image of G1 and the intensity transmission function of G2, and $\varphi_x(x, y)$ is the x component of $\varphi(x, y)$ given in Eq. (7). d is the period of G2, and χ is the displacement of one of the gratings against the other in the x direction. $\Delta(x, y)$ is introduced in Eq. (19), as it is in Eq. (8), to express the imperfection in grating fabrication and alignment.

Among diffracted waves created at G1, the 0th and ± 1 st orders are dominant. Then, the form of Eq. (19) is approximately the same as Eq. (8) described for two-beam interferometry. The fringe-scanning method mentioned in Section 2.2.2.1 is therefore available to retrieve $\varphi_x(x, y)$. By displacing G2 with a step of d/M , multiple moiré patterns are recorded. In Eq. (19), χ is replaced with kd/M , and the same procedure as Eq. (10) is applied [10]; that is,

$$\varphi_x(x, y) + \Delta(x, y) = \frac{d}{2\pi z} \arg \left[\sum_{k=1}^M I_k^G(x, y) \exp \left(-2\pi i \frac{k}{M} \right) \right], \quad (20)$$

where $I_k^G(x, y)$ is the image when $\chi = kd/M$. By displacing G1 instead of G2, $\varphi_x(x, y)$ can be determined in the same manner. More details on the image mapping refraction in addition to those mapping absorption and scattering are described later in Section 2.4.

The Fourier transform method described in Section 2.2.2.2 is also available when the self-image can be recorded (without G2) [34]. Furthermore, when a Talbot interferometer is constructed, fine rotation moiré fringes generated by inclining one of the gratings against the other can be used as carrier fringes [35].

To generate a moiré pattern by the Talbot interferometer, spatially

coherent X-rays are necessary; that is, collimated X-rays at synchrotron facilities or spherical-wave X-rays from a microfocus X-ray tube should be used. However, the limited X-ray flux available from a microfocus X-ray tube is not sufficient for clinical purposes. Although a conventional X-ray tube widely used for X-ray equipment at hospitals is preferable from the viewpoint of the measurement time for diagnosis, the moiré pattern (i.e., phase contrast) is not observed. To meet this demand, the Talbot-Lau interferometer was developed [11] by adding an amplitude grating (G0) to the Talbot interferometer, as shown in Fig. 3(b). When each slit of G0 is considered as a point source (strictly a line source), X-rays through the slit generate a moiré pattern at the Talbot interferometer (G1&G2) set downstream, as do X-rays through the neighboring slit. The period of G0 is designed so that all moiré patterns are overlapped constructively. Thus, the function of the Talbot interferometer is exhibited by the Talbot-Lau interferometer even with a conventional X-ray tube, allowing a measurement time acceptable from a clinical point of view. The procedure of phase imaging is identical to that for the Talbot interferometer.

The Talbot and Talbot-Lau interferometers use gratings whose period is below 10 μm to utilize interferometric phenomena (Talbot or fractional Talbot effect). Another similar approach with gratings (or masks) having a coarser period, which was called edge-illumination approach [36] and has subsequently been called the coded-aperture approach [37], is also studied. The shadow pattern of the mask cast on the detector is recorded. When a sample is placed between the mask and the image detector and another mask is placed in front of the image detector, the shadow edge is shifted by the X-ray refraction at the sample, and the change in the X-ray intensity is recorded by each detector pixel. By scanning the second mask, images similar to those by the Talbot and Talbot-Lau interferometers are generated. To ensure that a sufficiently sharper shadow edge is formed, an X-ray tube of a smaller focus size should be used. Although the Talbot-Lau interferometer does not require such a condition for operation, it is advantageous that the masks are fabricated more easily than the gratings needed for the Talbot-Lau interferometer.

Another attractive approach classified in this method is the method that analyses X-ray speckle patterns generated by cheap materials, such as a sandpaper [38,39]. This phenomenon corresponds to the contrast mentioned in Section 2.2.3; a speckle pattern is observed by the propagation-based approach for a material with random structures. When a sample is placed between a piece of sandpaper and an image detector, the speckle pattern is slightly deformed by the sample. By analysing the deformation with a correlation technique, images similar to those by the Talbot interferometer are generated. In this case, no optical element is used in front of the detector, and instead a high-resolution image detector must be employed to resolve the speckle

Fig. 3. Grating-based method: (a) Talbot interferometer and (b) Talbot-Lau interferometer.

feature.

2.3. X-ray phase tomography

X-ray computed tomography (CT) is extensively used in medicine to depict the inside of living bodies three dimensionally. Based on Eq. (2), by measuring D along multiple projection lines across an object, linear absorption coefficient $\mu(x, y, z)$ can be reconstructed. The same form as Eq. (2) is found for the phase shift in Eq. (4), which implies that $\delta(x, y, z)$ can be reconstructed by measuring Φ along the projection lines across an object using the same mathematical procedure as that for conventional X-ray CT [40]. By the approaches described in Sections 2.2.2 and 2.2.4, the differentiation of Φ (i.e., φ_x) is measured. In these cases, by using a Hilbert kernel in the filtered back-projection method [41], $\delta(x, y, z)$ can be reconstructed as well.

Fig. 4 shows a gallery of X-ray phase tomograms from the author's results obtained for biological soft tissues and a polymer blend [42–47]. Since the magnitude of f' in Eq. (5) is negligible for low-Z elements in the hard X-ray region, δ is approximately proportional to the electron density, which is furthermore approximated to the mass density. According to the results by using synchrotron radiation and a Bonse-Hart interferometer (Fig. 2(a)), a density deviation larger than 1 mg/cm³, which was evaluated by the standard deviation of noise, could be depicted [19,47].

Fig. 4. X-ray phase tomograms of biological tissues of rat kidney [42,43], mouse liver, rabbit liver [44], mouse artery [45], mouse tail [44], red maggot [46], and polystyrene/PMMA polymer blend sample [47]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.4. Scattering signal retrieval

Fig. 5 illustrates the change in the pixel value when a grating of a Talbot interferometer is displaced when the fringe-scanning method is applied. The change (so-called phase-stepping curve) is approximated as a sinusoidal curve and described by three independent parameters: $B_0^G(x, y)$, $B_1^G(x, y)$, and $\varphi_x(x, y)$. The meanings of $B_0^G(x, y)$ and $\varphi_x(x, y)$ were discussed above; that is, information of absorption and refraction (or differential phase) are involved, respectively. Here, the significance and usage of $B_1^G(x, y)$ are considered.

Because of the existence of an object, the oscillation amplitude of the phase-stepping curve occasionally decreases. To evaluate this effect, visibility $V(x, y) \equiv \{I_{\max}(x, y) - I_{\min}(x, y)\} / \{I_{\max}(x, y) + I_{\min}(x, y)\} = B_1^G(x, y) / B_0^G(x, y)$ is calculated, where $I_{\max}(x, y)$ and $I_{\min}(x, y)$ are the maximum and minimum values in the phase-stepping curve. This value is comparable to the visibility of moiré fringes. Specifically, to obtain $V(x, y)$ quickly,

$$V(x, y) = 2 \cdot \left| \sum_{k=1}^M I_k^G(x, y) \exp\left(-2\pi i \frac{k}{M}\right) \right| / \sum_{k=1}^M I_k^G(x, y) \quad (20)$$

can be used for the data by the fringe-scanning method, where $I_k^G(x, y)$ is the moiré pattern at the k th step.

This effect is mainly caused by small-angle X-ray scattering induced by the microstructures that exist in an object but are not resolved in $\varphi_x(x, y)$. Scattered X-rays no longer contribute to interference and $B_1^G(x, y)$ decreases as a result. Therefore, $V(x, y)$ is considered to be a map of the distribution of the microstructures. In other words, this signal is called the ‘dark-field’ signal [48]. Its magnitude depends on the density and size of the microstructures [49]. Roughly speaking, the signal is prominent for microstructures having a size corresponding to the grating period, and those of even larger or smaller sizes exhibit the signals but these signals are more suppressed. As shown in Fig. 5(d), fibrous tissues in a grape are depicted in $V(x, y)$. A similar signal can also be obtained by the approaches shown in Fig. 2(a) and 2(b) [50,51]. This signal is also used for tomography, and, assuming Lambert-Beer’s law, $V/V_0 = \exp(-\alpha T)$, where V_0 is the visibility without an object and α is introduced as the linear diffusion coefficient to describe its physical sense [52].

When the microstructures have anisotropic forms, the X-ray scattering varies depending on their orientation. Therefore, since the grating interferometer with linear gratings detects scattering in only one direction (the x direction in the abovementioned formalization), the dark-field signal varies when an object is rotated about the optical axis; that is, assuming that the variation is sinusoidal,

$$V(x, y) = V_0(x, y) + V_1(x, y) \cos[\Theta(x, y) + \omega], \quad (21)$$

where ω is the rotation angle about the optical axis. $\Theta(x, y)$ describes the anisotropy of the microstructures to be measured. By setting $\omega = \pi k/M$ ($k = 1, 2, \dots, M$),

$$V_k(x, y) = V_0(x, y) + V_1(x, y) \cos\left[\Theta(x, y) + \pi \frac{k}{M}\right], \quad (22)$$

is used for the analysis using the fringe-scanning method. $V_0(x, y)$ is the average visibility and $V_1(x, y)$ indicates the degree of anisotropy. This treatment is known as ‘vector radiography’ [53,54]. For instance, fibrous tissues in biological systems generate strong contrast in vector radiography.

3. Developments for clinical uses

As mentioned, X-ray phase-imaging techniques were initially developed mainly with synchrotron radiation. Following conceptual demonstrations of the abovementioned phase-imaging techniques, pre-clinical studies by using biological samples were extensively

Fig. 5. (a) Phase-stepping curve expressed by $B_0^G(x, y)$, $B_1^G(x, y)$, and $\phi_x(x, y)$. Images of (b) absorption, (c) differential phase (or refraction), and (d) visibility obtained with X-rays for a grape.

performed to understand the potential of X-ray phase imaging, as reviewed by A. Bravin [7]. After those activities, some attempts at moving onto clinical stages have been reported by applying the phase imaging to human patients. Here, such pilot works are introduced.

3.1. Mammography

The challenge of using the propagation-based method for mammography was first undertaken at Elettra Sincrotrone Trieste, Italy [9]. The system built at the SYRMEP beamline [55] was used with monochromatic X-rays in the range of 17–22 keV according to breast thickness and glandularity. Since synchrotron radiation is a horizontal laminar beam, a patient support platform was constructed so that a breast is scanned by moving the platform vertically. To gain phase contrast, an X-ray image detector was set 2 m downstream from the breast. The distance between the synchrotron source and the breast was 30 m. With this system, 47 women with questionable or suspicious breast abnormalities identified at combined digital mammography and ultrasonography were scanned. The resultant images were evaluated based on the Breast Imaging Reporting and Data System (BI-RADS). BI-RADS scores of 29 in the 31 patients whose abnormalities were finally diagnosed benign were 1–3. BI-RADS scores of 13 in the remaining 16 patients whose abnormalities were finally diagnosed malignant were 4–5. It was thus concluded that the synchrotron mammography system could be used to clarify cases of questionable or suspicious breast abnormalities.

As mentioned, however, the clinical use of the system developed at synchrotron radiation facilities is limited in terms of location and opportunity. Outside of synchrotron radiation facilities (i.e., in laboratories and hospitals), propagation-based phase contrast can be generated by using a microfocus X-ray tube [26]. The smaller the focus size is, the clearer the phase contrast is. However, microfocus X-ray tubes with a focus of several microns dedicated for materials science and engineering are not available for clinical purposes because the X-ray flux is low and an unacceptably long exposure time is necessary. The larger the focus size is, the shorter the exposure time is. Konica Minolta, Japan found a solution in using a Mo X-ray tube whose focus size is 0.1 mm in developing a mammography system [56]. The distance between the tube and an object was 0.65 m and the distance between the object and an imaging detector was 0.49 m. Although the setting was not ideal for phase contrast generation, the edge enhancement effect appearing at structural boundaries could be implemented to some extent for image quality improvement of conventional mammography. This development was conducted by industry (Konica Minolta, Japan) and it was later commercialized.

This achievement was a significant step, and the term ‘X-ray phase contrast’ was gradually recognized by radiologists in clinical practice. However, the phase-contrast effect was utilized merely to improve the contrast in conventional mammograms. Grating interferometry followed this development as the next step to further benefit from X-ray phase contrast.

3.2. Diagnosis of arthritis

In developing an apparatus based on the Talbot-Lau interferometer described in Section 2.2.4, X-ray transmission gratings must be prepared. The fabrication of G2 (see Fig. 3(b)) is especially challenging because three requirements must be satisfied simultaneously: (a) period of micrometer order, (b) thick pattern (several tens of microns or more in thickness even if Au is used as the pattern material), and (c) large area corresponding to the field of view (FOV) needed for diagnosis.

To meet these demands, X-ray lithography and gold electroplating were used. The detailed fabrication process is described in Refs. [57] and [58]. Following successful fabrication of G2 having a 60 mm × 60 mm area size, the early diagnosis of rheumatoid arthritis (RA) was selected as the first potential application target, assuming the scan over a part of a palm or a knee for depicting cartilage. Following preliminary study with a human cadaver that confirmed the correspondence of the features detected in differential phase images (i.e., $\phi_x(x, y)$) to anatomical findings [59,60], the system for diagnosing RA was developed [12,60].

Fig. 6. (a) X-ray phase-imaging system based on the Talbot-Lau interferometer installed in a hospital, and resultant (b) absorption image, (c) refraction (differential phase) image, (d) its zoomed image in the rectangle indicated in (c), and (e) visibility image of a part of the author's palm. The surface of the cartilage in the metacarpophalangeal joint of the second finger is revealed as indicated by the arrows in (d).

A photograph of the apparatus is shown in Fig. 6(a) with the author as an examinee. The upright-type apparatus has a normal X-ray tube emitting cone-beam X-rays downward. G0 is located in the box beneath the tube, and G1 and G2 are located in the other box under the table. A flat-panel detector is placed behind G2. The palm was fixed on the table by the holder to pull the fingers to open the gap of the joints moderately so that cartilage surfaces are not overlapped by bone features. The table can be combined with a bed extension on which a patient can lie so that the knee of the patient can also be imaged. For the phase imaging explained in Section 2.2.4, the three-step fringe-scanning method was employed. When the X-ray tube was operated with a tube voltage of 40 kVp and a tube current of 100 mA, the total scan time was 32 sec including 19-sec X-ray exposure. The average radiation skin dose was 5 mGy.

While no signal of cartilage was detected in the absorption image shown in Fig. 6(b), the surface of the cartilage in the metacarpophalangeal joint of the second finger was depicted in the differential phase image shown in Fig. 6(c) (and its zoomed image in Fig. 6(d)). The thickness of the cartilage and the smoothness of the cartilage surface are candidates for indicators for early diagnosis. The clinical significance of the differential phase image was studied for 140 joints in 70 RA patients and 110 joints in 55 healthy volunteers [61]. It was concluded that the apparatus had the potential for early RA diagnosis through the thickness measurement of cartilage, although further improvement of the apparatus is necessary; that is, shortening the exposure time, expanding the FOV, and increasing the tube voltage to image thicker body parts.

3.3. Diagnosis of lung diseases

The visibility (or dark-field) image shown in Fig. 6(e) was not discussed deeply because useful contrast of cartilage was not recognized for RA diagnosis. However, in *in vivo* mouse imaging, it was found that lungs produce significant contrast in dark-field images [62]. This result suggested the potential for diagnosis of chronic obstructive pulmonary disease (COPD) [63,64], lung fibrosis [65], and so on. In order to apply this approach for clinical purposes, a FOV covering the chest area of a human must be created. Since the technical hurdle is still high for covering a large FOV with a single grating, scanning schemes that move an object and an interferometer relatively are studied as an alternative [66–69]. In this development, one of the scanning schemes was adopted [70], and studies with human cadavers were then performed [71,72]. Although the details are not provided here, the procedure of the step-by-step sub-period grating movement needed for the fringe-scanning method can be omitted.

The developed apparatus is based on the Talbot-Lau interferometer. Since the size of the grating fabricated in the abovementioned manner is essentially smaller than 10 cm, 7 gratings were aligned in a line to cover a 40 cm width [70,71]. The grating size in the other direction is 2.5 cm, and the scanning approach was adopted; that is, the interferometer system was scanned across the chest area.

As a result, a 32 cm × 35 cm effective FOV was realized. An X-ray tube operated at 70 kVp and 400 mA with 12 Hz pulse frequency was employed, and the scan time over the FOV and the dose were 30 sec and 80 μSv. A similar system developed for human patients is in operation in a hospital, and a series of patient examinations is in progress [13].

4. Future prospects

From a physical point of view, the advantage of X-ray phase imaging over conventional X-ray radiography is obvious. However, the number of attempts at developing clinical apparatuses in hospitals can be counted on the fingers of one hand. Although the development of grating-based phase-contrast techniques with a laboratory-based X-ray tube was a significant breakthrough, it is necessary to overcome further technical difficulties in X-ray phase imaging, that is, fabricating gratings

with better properties, expanding the FOV, shortening the scan time, acquiring three-dimensional information (i.e., toward a tomographic scheme), and so on. Then, other application targets with X-ray phase imaging can be proposed.

Although not mentioned in Section 3.1, instrumentations for mammography are in progress using the grating-based approach. Following reports of imaging results of mastectomy specimens [73,74], installation of gratings into a mammography apparatus [68] has been reported. Examination results of the system by scanning patients are expected to be available in the near future.

From a medical point of view, a more extensive survey is needed for confirming the significance of diagnosis with X-ray phase imaging in terms of early-stage detection, grade of malignancy, medical treatment determination, patients' quality of life, and so on. The application trials introduced in this review have not reached sufficient conclusions, and further extensive study will be conducted.

It should be noted that the 1,000-fold gain of using the X-ray phase information shown in Fig. 1 is not reflected in phase-imaging apparatuses at it is. Depending on the approach of phase-contrast generation, the gain is reduced to some extent. As a result, absorption contrast looks better than phase contrast occasionally depending on samples and experimental parameters. In addition to the refinement of the known approaches of phase-contrast generation and phase measurement, it is expected that even newer approaches more suitable for clinical purposes will be achieved in the future and that X-ray phase imaging will be used more widely in clinics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Röntgen WC. Über eine neue Art von Strahlen. *Ann Phys* 1895;300:12–7.
- [2] Friedrich W, Knipping P, Laue M. Interferenz-Erscheinungen bei Röntgenstrahlen. *Bayer Akad Wiss München* 1912:303–22.
- [3] Zernike F. Inflection theory of the cutting method and its improved form, the phase contrast method. *Physica* 1934;1:689–704.
- [4] Fitzgerald R. Phase-Sensitive X-Ray Imaging. *Phys Today* 2000;53(7):23–6. <https://doi.org/10.1063/1.1292471>.
- [5] Momose A. Recent Advances in X-ray Phase Imaging. *Jpn. J. Appl. Phys.* 2005;44(9A):6355–67. <https://doi.org/10.1143/JJAP.44.6355>.
- [6] Nugent KA. Coherent methods in the X-ray sciences. *Adv Phys* 2010;59(1):1–99. <https://doi.org/10.1080/00018730903270926>.
- [7] Bravin A, Coan P, Suortti P. X-ray phase-contrast imaging: from pre-clinical applications towards clinics. *Phys. Med. Biol.* 2013;58(1):R1–35. <https://doi.org/10.1088/0031-9155/58/1/R1>.
- [8] Hounsfield GN. Computerized transverse axial scanning (tomography): Part I. Description of system. *Br J Radiol* 1973;46:1016–22.
- [9] Castelli E, Tonutti M, Arfelli F, Longo R, Quaia E, Rigon L, Sanabor D, Zanconati F, Dreossi D, Abrami A, Quai E, Bregant P, Casarin K, Chenda V, Menk RH, Rokvic T, Vascotto A, Tromba G, Cova MA. Mammography with Synchrotron Radiation: First Clinical Experience with Phase-Detection Technique. *Radiology* 2011;259(3):684–94. <https://doi.org/10.1148/radiol.11100745>.
- [10] Momose A, Kawamoto S, Koyama I, Hamaishi Y, Takai K, Suzuki Y. Demonstration of X-Ray Talbot Interferometry. *Jpn. J. Appl. Phys.* 2003;42(Part 2, No. 7B):L866–8. <https://doi.org/10.1143/JJAP.42.L866>.
- [11] Pfeiffer F, Weitkamp T, Bunk O, David C. Phase retrieval and differential phase-contrast imaging with low-brilliance X-ray sources. *Nature Phys* 2006;2(4):258–61. <https://doi.org/10.1038/nphys265>.
- [12] Momose A, Yashiro W, Kido K, Kiyohara J, Makifuchi C, Ito T, Nagatsuka S, Honda C, Noda D, Hattori T, Endo T, Nagashima M, Tanaka J. X-ray phase imaging: from synchrotron to hospital. *Phil. Trans. R. Soc. A.* 2014;372(2010):20130023. <https://doi.org/10.1098/rsta.2013.0023>.
- [13] Willer K, Fingerle A, Noichl W, De Marco F, Frank M, Urban T, Schick R, Gustschin A, Gleich B, Koehler T, Yaroshenko A, Pralow T, Zimmermann G, Renger B, Sauter A, Pfeiffer D, Rummeny E, Herzen J, Pfeiffer F. Dark-field chest X-rays – First patient trials. submitted.
- [14] Momose A, Fukuda J. Phase-contrast radiographs of nonstained rat cerebellar specimen. *Med. Phys.* 1995;22(4):375–9. <https://doi.org/10.1118/1.597472>.
- [15] X-Ray interactions with matter. Available online: http://henke.lbl.gov/optical_constants/.

- [16] Bonse U, Hart M. AN X-RAY INTERFEROMETER. *Appl. Phys. Lett.* 1965;6(8): 155–6. <https://doi.org/10.1063/1.1754212>.
- [17] Bruning JH, Herriott DR, Gallagher JE, Rosenfeld DP, White AD, Brangaccio DJ. Digital Wavefront Measuring Interferometer for Testing Optical Surfaces and Lenses. *Appl. Opt.* 1974;13(11):2693. <https://doi.org/10.1364/AO.13.002693>.
- [18] Takeda M, Ina H, Kobayashi S. Fourier-transform method of fringe-pattern analysis for computer-based topography and interferometry. *J. Opt. Soc. Am.* 1982;72(1): 156. <https://doi.org/10.1364/JOSA.72.000156>.
- [19] Momose A, Takeda T, Itai Y, Hirano K. Phase-contrast X-ray computed tomography for observing biological soft tissues. *Nat Med* 1996;2(4):473–5. <https://doi.org/10.1038/nm0496-473>.
- [20] *Two-dimensional phase unwrapping. Theory, algorithms, and software.* New York: John Wiley & Sons; 1998.
- [21] Davis TJ, Gao D, Gureyev TE, Stevenson AW, Wilkins SW. Phase-contrast imaging of weakly absorbing materials using hard X-rays. *Nature* 1995;373(6515):595–8. <https://doi.org/10.1038/373595a0>.
- [22] Ingal VN, Beliaevskaya EA. X-ray plane-wave topography observation of the phase contrast from a non-crystalline object. *J. Phys. D: Appl. Phys.* 1995;28(11):2314–7. <https://doi.org/10.1088/0022-3727/28/11/012>.
- [23] Chapman D, Thomlinson W, Johnston RE, Washburn D, Pisano E, Gmür N, Zhong Z, Menk R, Arfelli F, Sayers D. Diffraction enhanced x-ray imaging. *Phys. Med. Biol.* 1997;42(11):2015–25. <https://doi.org/10.1088/0031-9155/42/11/001>.
- [24] Authier A. *Dynamical theory of X-ray diffraction.* Oxford, New York; 2001.
- [25] Snigirev A, Snigireva I, Kohn V, Kuznetsov S, Schelokov I. On the possibilities of x-ray phase contrast microimaging by coherent high-energy synchrotron radiation. *Rev Sci Instrum* 1995;66(12):5486–92. <https://doi.org/10.1063/1.1146073>.
- [26] Wilkins SW, Gureyev TE, Gao D, Pogany A, Stevenson AW. Phase-contrast imaging using polychromatic hard X-rays. *Nature* 1996;384(6607):335–8. <https://doi.org/10.1038/384335a0>.
- [27] Cloetens P, Ludwig W, Baruchel J, Van Dyck D, Van Landuyt J, Guigay JP, Schlenker M. Holotomography: Quantitative phase tomography with micrometer resolution using hard synchrotron radiation x rays. *Appl. Phys. Lett.* 1999;75(19): 2912–4. <https://doi.org/10.1063/1.125225>.
- [28] Teague MR. Deterministic phase retrieval: a Green's function solution. *J. Opt. Soc. Am.* 1983;73(11):1434. <https://doi.org/10.1364/JOSA.73.001434>.
- [29] Gureyev TE, Raven C, Snigirev A, Snigireva I, Wilkins SW. Hard x-ray quantitative non-interferometric phase-contrast microscopy. *J. Phys. D: Appl. Phys.* 1999;32(5): 563–7. <https://doi.org/10.1088/0022-3727/32/5/010>.
- [30] Paganin D, Mayo SC, Gureyev TE, Miller PR, Wilkins SW. Simultaneous phase and amplitude extraction from a single defocused image of a homogeneous object. *J Microsc* 2002;206(1):33–40. <https://doi.org/10.1046/j.1365-2818.2002.01010.x>.
- [31] Talbot H. Facts relating to optical science. *Phil Mag* 1836;9:401–7.
- [32] Winthrop JT, Worthington CR. Theory of Fresnel Images I Plane Periodic Objects in Monochromatic Light*. *J. Opt. Soc. Am.* 1965;55(4):373. <https://doi.org/10.1364/JOSA.55.000373>.
- [33] Guigay JP. On Fresnel Diffraction by One-dimensional Periodic Objects, with Application to Structure Determination of Phase Objects. *Optica Acta: International Journal of Optics* 1971;18(9):677–82. <https://doi.org/10.1080/713818491>.
- [34] Takeda Y, Yashiro W, Suzuki Y, Aoki S, Hattori T, Momose A. X-Ray Phase Imaging with Single Phase Gratings. *Jpn. J. Appl. Phys.* 2007;46(N0. 3):L89–91. <https://doi.org/10.1143/JJAP.46.L89>.
- [35] Momose A, Yashiro W, Maikusa H, Takeda Y. High-speed X-ray phase imaging and X-ray phase tomography with Talbot interferometer and white synchrotron radiation. *Opt. Express* 2009;17(15):12540. <https://doi.org/10.1364/OE.17.012540.m005>.
- [36] Olivo A, Arfelli F, Cantatore G, Longo R, Menk RH, Pani S, Prest M, Poropat P, Rigon L, Tromba G, Vallazza E, Castelli E. An innovative digital imaging set-up allowing a low-dose approach to phase contrast applications in the medical field. *Med. Phys.* 2001;28(8):1610–9. <https://doi.org/10.1118/1.1388219>.
- [37] Olivo A, Speller R. A coded-aperture technique allowing x-ray phase contrast imaging with conventional sources. *Appl. Phys. Lett.* 2007;91(7):074106. <https://doi.org/10.1063/1.2772193>.
- [38] Morgan KS, Paganin DM, Siu KKW. X-ray phase imaging with a paper analyzer. *Appl. Phys. Lett.* 2012;100(12):124102. <https://doi.org/10.1063/1.3694918.1>.
- [39] Berujon S, Wang H, Sawhney K. X-ray multimodal imaging using a random-phase object. *Phys. Rev. A* 2012;86(6). <https://doi.org/10.1103/PhysRevA.86.063813>.
- [40] Momose A. Demonstration of phase-contrast X-ray computed tomography using an X-ray interferometer. *Nucl Instrum Methods Phys Res, Sect A* 1995;352(3):622–8. [https://doi.org/10.1016/0168-9002\(95\)90017-9](https://doi.org/10.1016/0168-9002(95)90017-9).
- [41] Faris GW, Byer RL. Three-dimensional beam-deflection optical tomography of a supersonic jet. *Appl. Opt.* 1988;27(24):5202. <https://doi.org/10.1364/AO.27.005202>.
- [42] Momose A. Phase-sensitive imaging and phase tomography using X-ray interferometers. *Opt. Express* 2003;11(19):2303. <https://doi.org/10.1364/OE.11.002303>.
- [43] Wu J, Takeda T, Thet Lwin T, Momose A, Sunaguchi N, Fukami T, Yuasa T, Akatsuka T. Imaging renal structures by X-ray phase-contrast microtomography. *Kidney Int* 2009;75(9):945–51. <https://doi.org/10.1038/ki.2009.42>.
- [44] Momose A, Yashiro W, Takeda Y, Suzuki Y, Hattori T. Phase Tomography by X-ray Talbot Interferometry for Biological Imaging. *Jpn. J. Appl. Phys.* 2006;45(6A): 5254–62. <https://doi.org/10.1143/JJAP.45.5254>.
- [45] Shinohara M, Yamashita T, Tawa H, Takeda M, Sasaki N, Takaya T, Toh R, Takeuchi A, Ohigashi T, Shinohara K, Kawashima S, Yokoyama M, Hirata K-I, Momose A. Atherosclerotic plaque imaging using phase-contrast X-ray computed tomography. *American Journal of Physiology-Heart and Circulatory Physiology* 2008;294(2):H1094–100. <https://doi.org/10.1152/ajpheart.01149.2007>.
- [46] Momose A, Yashiro W, Harasse S, Kuwabara H, Kawabata K. Four-dimensional X-ray phase tomography with Talbot interferometer and white synchrotron light. *Proc SPIE* 2010;7804:780405.
- [47] Momose A, Fujii A, Kadowaki H, Jinnai H. Three-Dimensional Observation of Polymer Blend by X-ray Phase Tomography. *Macromolecules* 2005;38(16): 7197–200. <https://doi.org/10.1021/ma050917o>.
- [48] Pfeiffer F, Bech M, Bunk O, Kraft P, Eikenberry EF, Brönnimann Ch, Grünzweig C, David C. Hard-X-ray dark-field imaging using a grating interferometer. *Nature Mater* 2008;7(2):134–7. <https://doi.org/10.1038/nmat2096>.
- [49] Yashiro W, Terui Y, Kawabata K, Momose A. On the origin of visibility contrast in x-ray Talbot interferometry. *Opt. Express* 2010;18(16):16890. <https://doi.org/10.1364/OE.18.016890>.
- [50] Yoneyama A, Takeda T, Tsuchiya Y, Wu J, Lwin T-T, Hyodo K. Coherence-contrast x-ray imaging based on x-ray interferometry. *Appl. Opt.* 2005;44(16):3258. <https://doi.org/10.1364/AO.44.003258>.
- [51] Wernick MN, Wirjadi O, Chapman D, Zhong Z, Galatsanos NP, Yang Y, Brankov JG, Oltulu O, Anastasio MA, Muehleman C. Multiple-image radiography. *Phys. Med. Biol.* 2003;48(23):3875–95. <https://doi.org/10.1088/0031-9155/48/23/006>.
- [52] Bech M, Bunk O, Donath T, Feidenhans'l R, David C, Pfeiffer F. Quantitative x-ray dark-field computed tomography. *Phys. Med. Biol.* 2010;55(18):5529–39. <https://doi.org/10.1088/0031-9155/55/18/017>.
- [53] Jensen TH, Bech M, Bunk O, Donath T, David C, Feidenhans'l R, Pfeiffer F. Directional x-ray dark-field imaging. *Phys. Med. Biol.* 2010;55(12):3317–23. <https://doi.org/10.1088/0031-9155/55/12/004>.
- [54] Potdevin G, Malecki A, Biernath T, Bech M, Jensen TH, Feidenhans'l R, Zanette I, Weitkamp T, Kenntner J, Mohr J, Roschger P, Kerschnitzki M, Wagermaier W, Klaushofer K, Fratzl P, Pfeiffer F. X-ray vector radiography for bone micro-architecture diagnostics. *Phys. Med. Biol.* 2012;57(11):3451–61. <https://doi.org/10.1088/0031-9155/57/11/3451>.
- [55] Dreossi D, Abrami A, Arfelli F, Bregant P, Casarin K, Chenda V, Cova MA, Longo R, Menk R-H, Quai E, Quaia E, Rigon L, Rokvic T, Sanabor D, Tonutti M, Tromba G, Vascotto A, Zanconati F, Castelli E. The mammography project at the SYRMEP beamline. *Eur J Radiol* 2008;68(3):S58–62. <https://doi.org/10.1016/j.ejrad.2008.04.038>.
- [56] Tanaka T, Honda C, Matsuo S, Noma K, Ohara H, Nitta N, Ota S, Tsuchiya K, Sakashita Y, Yamada A, Yamasaki M, Furukawa A, Takahashi M, Murata K. The First Trial of Phase Contrast Imaging for Digital Full-Field Mammography Using a Practical Molybdenum X-Ray Tube. *Invest Radiol* 2005;40(7):385–96. <https://doi.org/10.1097/01.rli.0000165575.43381.48>.
- [57] Matsumoto M, Takiguchi K, Tanaka M, Hunabiki Y, Takeda H, Momose A, Utsumi Y, Hattori T. Fabrication of diffraction grating for X-ray Talbot interferometer. *Microsyst Technol* 2007;13(5-6):543–6. <https://doi.org/10.1007/s00542-006-0226-8>.
- [58] Mohr J, Grund T, Kunka D, Kenntner J, Leuthold J, Meiser J, et al. High aspect ratio gratings for X-ray phase contrast imaging. *AIP Conf Proc* 2012;1466:41–50.
- [59] Nagashima M, Tanaka J, Kiyohara J, Makifuchi C, Kido K, Momose A. Application of X-ray grating interferometry for the imaging of joint structures. *Anat Sci Int* 2014;89(2):95–100. <https://doi.org/10.1007/s12565-013-0204-z>.
- [60] Tanaka J, Nagashima M, Kido K, Hoshino Y, Kiyohara J, Makifuchi C, Nishino S, Nagatsuka S, Momose A. Cadaveric and in vivo human joint imaging based on differential phase contrast by X-ray Talbot-Lau interferometry. *Zeitschrift für Medizinische Physik* 2013;23(3):222–7. <https://doi.org/10.1016/j.zemedi.2012.11.004>.
- [61] Yoshioka H, Kadono Y, Kim YT, Oda H, Maruyama T, Akiyama Y, Mimura T, Tanaka J, Niitsu M, Hoshino Y, Kiyohara J, Nishino S, Makifuchi C, Takahashi A, Shinden Y, Matsusaka N, Kido K, Momose A. Imaging evaluation of the cartilage in rheumatoid arthritis patients with an x-ray phase imaging apparatus based on Talbot-Lau interferometry. *Sci Rep* 2020;10(1). <https://doi.org/10.1038/s41598-020-63155-9>.
- [62] Bech M, Tapfer A, Velroyen A, Yaroshenko A, Pauwels B, Hostens J, Bruyndonckx P, Sasov A, Pfeiffer F. In-vivo dark-field and phase-contrast x-ray imaging. *Sci Rep* 2013;3(1). <https://doi.org/10.1038/srep03209>.
- [63] Schleede S, Meinel FG, Bech M, Herzen J, Achterhold K, Potdevin G, Malecki A, Adam-Neumair S, Thieme SF, Bamberg F, Nikolaou K, Bohla A, Yildirim AO, Loewen R, Gifford M, Ruth R, Eickelberg O, Reiser M, Pfeiffer F. Emphysema diagnosis using X-ray dark-field imaging at a laser-driven compact synchrotron light source. *Proc Natl Acad Sci* 2012;109(44):17880–5. <https://doi.org/10.1073/pnas.1206684109>.
- [64] Hellbach K, Yaroshenko A, Meinel FG, Yildirim AO, Conlon TM, Bech M, Mueller M, Velroyen A, Notohamiprodjo M, Bamberg F, Auweter S, Reiser M, Eickelberg O, Pfeiffer F. In Vivo Dark-Field Radiography for Early Diagnosis and Staging of Pulmonary Emphysema. *Invest Radiol* 2015;50(7):430–5. <https://doi.org/10.1097/RLI.0000000000000147>.
- [65] Yaroshenko A, Hellbach K, Yildirim AO, Conlon TM, Fernandez IE, Bech M, Velroyen A, Meinel FG, Auweter S, Reiser M, Eickelberg O, Pfeiffer F. Improved In vivo Assessment of Pulmonary Fibrosis in Mice using X-Ray Dark-Field Radiography. *Sci Rep* 2015;5(1). <https://doi.org/10.1038/srep17492>.
- [66] Kottler C, Pfeiffer F, Bunk O, Grünzweig C, David C. Grating interferometer based scanning setup for hard x-ray phase contrast imaging. *Rev. Sci. Instrum.* 2007;78(4):043710. <https://doi.org/10.1063/1.2723064>.
- [67] Arboleda C, Wang Z, Stapanioni M. Tilted-grating approach for scanning-mode X-ray phase contrast imaging. *Opt. Express* 2014;22(13):15447. <https://doi.org/10.1364/OE.22.015447>.

- [68] Koehler T, Daerr H, Martens G, Kuhn N, Löscher S, van Stevendaal U, Roessl E. Slit-scanning differential x-ray phase-contrast mammography: Proof-of-concept experimental studies: Slit-scanning differential x-ray phase-contrast mammography. *Med. Phys.* 2015;42(4):1959–65. <https://doi.org/10.1118/1.4914420>.
- [69] Bachche S, Nonoguchi M, Kato K, Kageyama M, Koike T, Kuribayashi M, Momose A. Laboratory-based X-ray phase-imaging scanner using Talbot-Lau interferometer for non-destructive testing. *Sci Rep* 2017;7(1). <https://doi.org/10.1038/s41598-017-07032-y>.
- [70] Gromann LB, De Marco F, Willer K, Noël PB, Scherer K, Renger B, Gleich B, Achterhold K, Fingerle AA, Muenzel D, Auweter S, Hellbach K, Reiser M, Baehr A, Dmochewicz M, Schroeter TJ, Koch FJ, Meyer P, Kunka D, Mohr J, Yaroshenko A, Maack H-I, Pralow T, van der Heijden H, Proksa R, Koehler T, Wieberneit N, Rindt K, Rummeny EJ, Pfeiffer F, Herzen J. In-vivo X-ray Dark-Field Chest Radiography of a Pig. *Sci Rep* 2017;7(1). <https://doi.org/10.1038/s41598-017-05101-w>.
- [71] Willer K, Fingerle AA, Gromann LB, De Marco F, Herzen J, Achterhold K, Gleich B, Muenzel D, Scherer K, Renz M, Renger B, Kopp F, Kriner F, Fischer F, Braun C, Auweter S, Hellbach K, Reiser MF, Schroeter T, Mohr J, Yaroshenko A, Maack HI, Pralow T, van der Heijden H, Proksa R, Koehler T, Wieberneit N, Rindt K, Rummeny EJ, Pfeiffer F, Noël PB. X-ray dark-field imaging of the human lung—A feasibility study on a deceased body. *PLoS One* 2018;13:e0204565.
- [72] Fingerle AA, De Marco F, Andrejewski J, Willer K, Gromann LB, Noichl W, Kriner F, Fischer F, Braun C, Maack H-I, Pralow T, Koehler T, Noël PB, Meurer F, Deniffel D, Sauter AP, Haller B, Pfeiffer D, Rummeny EJ, Herzen J, Pfeiffer F. Imaging features in post-mortem x-ray dark-field chest radiographs and correlation with conventional x-ray and CT. *Eur Radiol Exp* 2019;3(1). <https://doi.org/10.1186/s41747-019-0104-7>.
- [73] Stampanoni M, Wang Z, Thüning T, David C, Roessl E, Trippel M, Kubik-Huch RA, Singer G, Hohl MK, Hauser N. The First Analysis and Clinical Evaluation of Native Breast Tissue Using Differential Phase-Contrast Mammography: *Invest Radiol* 2011;46(12):801–6. <https://doi.org/10.1097/RLL.0b013e31822a585f>.
- [74] Wang Z, Hauser N, Singer G, Trippel M, Kubik-Huch RA, Schneider CW, Stampanoni M. Non-invasive classification of microcalcifications with phase-contrast X-ray mammography. *Nat Commun* 2014;5(1). <https://doi.org/10.1038/ncomms4797>.