Development of phase-contrast X-ray imaging techniques and potential medical applications

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Abstract A significant improvement over conventional attenuation-based X-ray imaging, which lacks contrast in small objects and soft biological tissues, is obtained by introducing phase-contrast imaging. As recently demonstrated, phase-contrast imaging is characterized by its extraordinary image quality, greatly enhanced contrast, and good soft tissue discrimination with very high spatial resolution down to the micron and even the sub-micron region. The rapid development of compact X-ray sources of high brightness, tuneability, and monochromaticity as well as high-resolution X-ray detectors with high quantum efficiency and improved computational methods is stimulating the development of a new generation of X-ray imaging systems for medical applications. The present paper reviews some intrinsic mechanisms, recent technical developments and potential medical applications of two-, three- and four-dimensional phase-contrast X-ray imaging. Challenging issues in current phase-contrast imaging techniques and key clinical applications are discussed and possible developments of future high-contrast and high spatial and temporal resolution medical X-ray imaging systems are outlined.

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Introduction

Diagnostic X-rays are an electromagnetic radiation with photon energies in the range from about 0.1 keV to several hundreds of keV. For medical imaging applications, the photon energy of the X-ray is normally within the range of 10–200 keV. The very short wavelength (0.1–1.0 Å) makes the X-ray an excellent probe to study small objects, structures in different media and not least biological tissues. When an X-ray photon impinges upon a biological sample, it may be absorbed, scattered in one or more interactions, or traverse the tissue without interaction. In diagnostic radiography, three interaction processes of X-ray photon transport in tissues are of particular importance, namely the coherent Rayleigh scattering, the photoelectric absorption, and the incoherent Compton scattering. To image tissues of the body, conventional attenuation-based X-ray imaging methods are dominating the clinical use today. Since most soft tissues are almost equally transparent to hard X-rays, they are often not as
sensitive as magnetic resonance imaging (MRI). Mammography and X-ray angiography are typical examples where improved contrast is desirable. Furthermore, in the attenuation-based X-ray imaging, explicit information about photon scattering is ignored or eliminated, even if it may play an important role for tissue characterization [1–3]. As a result of coherent X-ray scattering, information about coherent phase changes of X-rays propagating in soft tissues may also play a significant role in diagnostic radiology. In fact, phase-contrast methods were first introduced into optical microscopy by Zernike in 1930s [4,5].

X-ray phase-contrast was reported in the middle of 1990s, and since then, phase-contrast X-ray imaging techniques have been extensively studied in recent years, especially for their potential biomedical applications [6,7].

The significance of phase-contrast in X-ray imaging of soft tissues may be understood in the classical framework of electromagnetic interactions in matter, where optical properties of biological tissues can be characterized by their refractive index. Different from conventional visible light optics, the refractive index in X-ray optics is very close to and smaller than unity since the X-ray photon energy is often much larger than the atomic resonance energies. In the first approximation, if the anisotropy of the medium is small and negligible, the refractive index characterizing the optical properties of the tissue can be expressed by taking into account the X-ray absorption in the complex form: \( n = 1 - \delta - i\beta \), in which \( \delta \) is the decrement of the real part of the refractive index, characterizing the phase shifting property, while the imaginary part \( \beta \) characterizes the absorption property of the tissue. In conventional attenuation-based radiography, the X-ray phase shift information is not directly utilized in the image reconstruction. However, at photon energies greater than 10 keV and for soft tissues made up of light elements, the phase shift term may play a more important role than the attenuation term in the X-ray imaging since \( \delta \) is typically three orders of magnitude larger than \( \beta \) as seen in Fig. 1. As a result, phase-contrast modalities can generate significantly greater image contrast compared to conventional radiography. Furthermore, far from absorption edges, \( \delta \) is inversely proportional to the square of the X-ray energy whilst \( \beta \) decreases as the fourth power of energy. Some numerical values of \( \delta \) and \( \beta \) for the complex refractive index of the breast tissue at different photon energy levels have been reported [6], indicating that the amount of phase-contrast relative to attenuation contrast increases with X-ray energy. The dependence of the ratio of \( \delta/\beta \) on X-ray photon energy is shown in Fig. 1 for breast tissue, water and cortical bone. Relative importance of some major interaction mechanisms of X-rays with a matter to the total mass attenuation coefficient in water (H2O) is also shown illustratively in the figure. Further discussion on these X-ray interaction mechanisms may be found in the literature [8,9]. Here, we have made use of the relations: \( \beta = \frac{1}{4\pi}\frac{\mu}{\rho} \) and \( \delta = 1.36 \times 10^{-10}\rho \lambda^2 \) where \( \mu \) is the linear absorption coefficient \((\text{cm}^{-1})\), \( \lambda \) the X-ray wavelength \((\text{cm})\), and \( \rho \) the density of the object \( (\text{g/cm}^3) \) [7]. Basic numerical data are taken from NIST database [10] for X-ray mass attenuation coefficients. It is seen that the phase-contrast is large at around 20–80 keV for soft tissues.

![Figure 1](image_url) Dependence of the phase to attenuation contrast parameter ratio \( (\delta/\beta) \) for breast tissue, water and cortical bone as well as dependence of the mass attenuation coefficients of water (H2O) and cortical bone on X-ray photon energy. Here, relevant numerical data are taken from NIST database for X-ray mass attenuation coefficients. It is seen that the phase-contrast is large at around 20–80 keV for soft tissues.

The refraction, the radiation dose may potentially be reduced by using for instance higher energy X-rays than commonly used for attenuation contrast. This could be of particular importance for the development of novel X-ray imaging techniques with high-contrast and low dose to the patients since more X-rays pass through the object without local energy deposition at high energies.

Like all new techniques, the introduction of modern imaging methods into clinical applications will be a challenge, trying to identify all new advantages as well as limitations. On one hand, technological progresses with new X-ray sources, high quantum efficiency X-ray detectors, microsystem technology as well as digital image-processing techniques are providing an excellent technological base for the development of refractive and phase-contrast X-ray imaging systems. On the other hand, medical applications of such novel imaging systems demand stringent conditions to be fulfilled, such as the limiting dose of radiation and detrimental effects, flash time of imaging, system reliability, and proper image processing so that details visualized by phase-contrast images can be easily identified as known lesions or medical conditions. Moreover, nowadays imaging is no longer limited to the purpose of medical diagnosis, but is becoming increasingly important for image-guided interventions as well as for functional assessments, such as...
perfusion, flow rate, diffusion, oxygen concentration, metabolism, etc. Thus, there appears an increasing demand for three-dimensional (3D) and four-dimensional (4D) (3D + time) imaging systems. Great interdisciplinary efforts are required to investigate optimal applications and solutions for advanced future medical X-ray imaging systems. In the following sections, some of recent technological developments and potential medical applications of the phase-contrast X-ray imaging techniques are reviewed and some system prospects for future medical X-ray imaging are outlined.

Phase-contrast X-ray imaging techniques

For soft biological tissues, such as most normal tissues and tumours, conventional attenuation-based X-ray imaging methods have not been very successful without the need to use contrast agents or CT approaches since these soft tissues often lack sufficient contrast. Mammography and angiography are two typical examples, in which the conventional X-ray imaging methods are challenged. Interestingly, phase-contrast X-ray imaging is sensitive to light elements such as hydrogen, carbon, nitrogen and oxygen found commonly in soft biological tissues. The phase-contrast arises because both the amplitude and phase are modified as an X-ray beam propagates through a tissue object. Since the probability for X-ray phase shift can be 1000 times larger than for X-ray attenuation in the keV energy range, phase-contrast imaging permits visualization of soft tissues that have identical or similar attenuation characteristics which are not detectable by use of conventional attenuation-based X-ray imaging methods. Moreover, because the refractive index-based image contrast decreases less rapidly with increasing X-ray energy than attenuation-based contrast, phase-contrast imaging will allow a reduction of the radiation dose delivered to the object studied [11]. Also, the increased contrast on its own will allow a dose decrease since a large noise level can be tolerated without severe loss of image details. Recently, phase-contrast X-ray imaging particularly using synchrotron radiation and some of new techniques have been developed considerably and will be reviewed here.

In-line phase-contrast X-ray imaging

The in-line phase-contrast X-ray imaging method, sometimes also called the propagation-based imaging or the in-line holography, exploits the Fresnel diffraction and dubbed phase-contrast imaging method, which was explored early by Snigirev and co-workers at ESRF [12] and by Wilkins and colleagues at CSIRO [13]. With this method, X-rays transmitted through the sample object at various angles will propagate over a certain distance between the object and the detector. Variations in thickness and X-ray refractive indices. Because there is also a change of X-ray attenuation across these interfaces, the effect of the phase-contrast imaging is to provide a variable enhancement of the conventional attenuation image. The edge-enhanced contrast has its importance in, for instance, image-guided radiation therapy, where one requires accurate positioning of targeted tissue volumes, such as tumours, which is often difficult to be achieved by conventional attenuation-based imaging since it often lacks edge contrast between soft tissues.

Fig. 2 shows illustratively a scheme of the in-line phase-contrast imaging method, in contrast to the conventional method of obtaining absorption images (Fig. 2(a)). In Fig. 2(b), \( R_1 \) denotes the source-object distance and \( R_2 \) is the object-image detector distance. \( W_1 \) is the first wavefront and \( W_2 \) is the second wavefront. \( l \) is the detected X-ray photon intensity. With this imaging modality, it is possible to use polychromatic X-ray sources. In order to achieve phase-contrast imaging based on diffraction effects, the X-ray source should, however, provide a sufficient degree of spatial or lateral coherence, which can be characterized by the spatial (lateral) coherence width \( L_{\text{coh}} \) of the source: \( L_{\text{coh}} = \lambda R_1/s \), where \( \lambda \) is the wavelength of the X-ray, \( R_1 \) is the distance between the source and the sample object, and \( s \) is the focal spot size of the X-ray source. It can be noticed here that the spatial coherence width \( L_{\text{coh}} \) decreases with increasing X-ray photon energy. This implies that better edge-enhancing efficiency can be achieved by a longer distance \( R_1 \), or lower photon energy for a given geometric configuration.

The required free space (air gap) over a distance \( R_2 \) from the object to the image detector plays also an important role in forming phase-contrast images. Illustratively, Fig. 3 shows how the image contrast may depend on the distance \( R_2 \). Theoretical guide for clinical implementation of this technique have been developed [14,15]. In particular, it was argued that in addition to the lateral coherence length \( L_{\text{coh}} \), the phase-space shearing length, defined by

![Figure 2](Image 2) Schemes of (a) an attenuation-based imaging configuration and (b) an in-line phase-contrast imaging configuration.
free space distance $d_{\text{shear}} = \beta R_2 |u| / M$, plays also an important role in phase-contrast visibility [16]. Here, $u$ denotes the spatial frequency of the structural component of the object and $M$ is the geometrical magnification factor, defined by $M = (R_1 + R_2) / R_1$. According to Wu and Liu [16], if the ratio of $L_{\text{shear}} / L_{\text{coh}}$ is much less than one, the wave field is almost fully coherent over the shearing length, and the phase-contrast associated with this structure component is visible. But if $L_{\text{shear}} / L_{\text{coh}}$ is much larger than one, the wave field is incoherent over the shearing length, and the phase-contrast associated with this structure component is invisible. For intermediate cases with $L_{\text{shear}} / L_{\text{coh}} < 1$, the wave field is almost partially coherent and phase-contrast visibility increases with decreasing $L_{\text{shear}}$. Obviously, the distance $R_2$ is a system parameter to be optimised. Besides, an appropriate free space distance $R_2$ in the in-line phase-contrast imaging has also an advantage of providing scatter rejection without the need for an anti-scatter grid and thus lower doses may result in similar image quality in comparison with conventional radiography, where the anti-scatter grid is normally used at the cost of an increased exposure time.

To retrieve the phase information from detected signal, a theoretical formalism has been introduced for the in-line phase-contrast imaging [17–19]. Normally two exposures are needed by changing the location of the image detector to obtain, respectively, the absorption image ($M = 1$) and the phase-contrast image ($M > 1$), from which both the amplitude and phase map of the X-ray intensity can be retrieved. To reduce the dose for medical imaging systems, two detectors have been suggested, requiring only a single exposure [20]. In practice, due to limited resolution of X-ray detectors, it is helpful to make use of the geometrical magnification factor $M$ in the design of the in-line phase-contrast imaging system set-up. However, care has to be taken for the effect of geometric blurring, which can be estimated as $s_{R_2} = R_2 / R_1$ [21]. By using an extended $R_2$ distance, there is a danger of increasing the geometric blurring to such an extent that the final image is degraded whether phase-contrast information has been recorded or not. There is, however, a report stating that magnification may increase sharpness by a rescaling effect, which is in competition with the geometric unsharpness in digital mammography [22].

Due to its simplicity, the in-line phase-contrast imaging method is very simple for potential clinical use and encouraging results have been reported in experiments. In fact, based essentially on the in-line phase-contrast imaging methodology and tissue refractive properties, the first clinical phase-contrast mammography system has been developed at Konica Minolta Medical & Graphic, Inc. [23] by using a practical molybdenum X-ray tube with a focal sport size of 0.1 mm. The resulting images have shown an edge enhancement at object interfaces with different refractive indices.

As we know, to get an image of sufficient quality is important in medical imaging. To understand image messages and be able to do medical diagnosis are even more important and challenging from the point view of clinical usages of the imaging system. At present, there still exist questions if the method could be used with sufficiently good image quality under clinical conditions for thick biological samples, which are important in medical imaging with strictly regulated dose limitations. Obviously, for thick biological tissues of clinical importance, overlapping structures may be difficult to resolve and will have varying amount of phase-contrast. A simply one-to-one relation between the object and image may not exist. Indeed, it was shown by some experiments that when the object is thicker, the image may lose its feature [24]. One obvious way to circumvent the problem of overlapping is to use a computed tomography (CT) technique. Synchrotron radiation tomography may provide a high-resolution of 3D structures. However, this technique may have problems when applied to live bodies since the exposure time tends to be too long (order of minutes or hours). Some efforts have been made for low-dose phase-contrast X-ray imaging by introducing, for instance, an intensifier screen [11].

Figure 3 Dependence of in-line phase-contrast images on the distance between object and detector. Here, given numerical data for $R_2$ are only illustrative, which, in practice, will depend on the specific system set-up, as discussed in the text.
Further efforts are, however, required to optimize the imaging system for medical applications, including efficient phase retrieval algorithms, limited angle reconstruction, stereography, and X-ray photon detectors of high-resolution and high detective quantum efficiency (DQE).

**Diffraction-enhanced X-ray imaging**

Diffraction-enhanced X-ray imaging (DEI) was explored early at the X-ray Laboratory in St. Petersburg by Ingal and Beliaevskaya [25], and at CSIRO by Wilkins and colleagues [26] as well as at NSLS by Chapman and co-workers [27,28]. DEI makes use of collimated X-ray beams produced by a perfect crystal monochromator and an analyzer crystal placed between the object and the detector, as shown in Fig. 4 [7,29,30]. In this approach, an incident monochromatic X-ray beam traverses the object and may undergo refraction due to refractive index gradients present in the object. This deflects the path of the X-ray beam by a small amount. For X-ray energies of interest in medical imaging, this deflection angle is very small, normally of the order of micro-radians. The X-rays may also be attenuated by the absorption in the object along the path, and may undergo scattering at larger angles. All these processes may have their effects on the image quality.

An important feature of the DEI system shown in Fig. 4 is that the analyzer, a perfect crystal, can be tuned to various angles. A monochromatic X-ray beam passes through the sample object and falls upon the analyzer crystal. Since the X-ray diffraction is coherent scattering of X-rays by atoms in the perfect crystal, and the wavelength of photons with energy of order 10 keV or higher is a little smaller than the spacing of atoms, the crystal acts as a sort of diffraction grating for the X-rays. Thus, the X-rays are diffracted and eventually impinge onto the detector surface only if they satisfy the Bragg condition at which the scattered X-rays interact with each other to create constructive interference. In other words, only X-rays aligned within the angle acceptance of the crystal analyzer will be diffracted onto the detector. This angular acceptance is called the rocking curve of the crystal [31].

The graph of the rocking curve for the diffracted X-ray intensity versus angle of the crystal has an approximately Gaussian shape, as shown illustratively in Fig. 5, in which the rocking angle \( \theta \) is relative to the Bragg angle \( \theta_0 \) of the crystal. This rocking curve is a reflectivity characteristic of the analyzer crystal, which varies very strongly with the angle of beam incidence over a few micro-radians. The slope of this curve converts effectively the X-ray phase shifts and resulting angular changes into intensity variations.

The use of different Bragg reflections with differing rocking curve gradients allows the sensitivity of the phase to intensity conversion to be adjusted. By altering the angle of the analyzer crystal, it is possible to record different refraction angles, and by doing so, it is possible to extract both the phase and absorption components from a number of images. The narrow rocking curve width of the analyzer crystal implies that it is also a very efficient mechanism for rejecting X-rays scattered at large angles. For instance, if the analyzer angle is set at the peak of the rocking curve, then an absorption image is retrieved that is free of scattered X-ray photons, provided that the scatter angle is larger than the width of the rocking curve. If the angle of the analyzer is set to one that yields an intensity corresponding to half of that at the peak of the rocking curve, then the reflectivity for X-rays that pass through the object undeviated is 50%. Deflected X-rays will be reflected with lower or higher efficiency depending on the angle they have when they fall upon the analyzer crystal relative to the rocking curve, as shown in Fig. 5 (see also Ref. [30] for some more detailed description).

Here, images recorded by a detector will contain information about the absorption, refraction and scattering characteristics of the sample object. By combining images (intensities) taken at the low angle side and the high angle side of the rocking curve, one may obtain the apparent absorption image and the refraction angle image [27]. The refraction angle image is quite sensitive to refraction effects on the X-rays. The contrast of the refraction angle image depends on thickness gradients of the tissue sample, a feature that strongly highlights the edges of the object, while the absorption image depends on linear integration of tissue absorption and thus the thickness of the object [32]. The complimentary behaviour of the refraction and absorption images is an advantage of the DEI technique in determining the extension of tumour growth. The spatial

**Figure 4** Schematic set-up of a diffraction-enhanced X-ray imaging system with a synchrotron beam. In the figure, the crystal analyzer is drawn to correspond with the high angle case \( (\theta > 0) \) of Fig. 5.
resolution of synchrotron-based DEI imaging has already reached the order of micrometers [33], which is several orders of magnitude higher than that of conventional CT or magnetic resonance imaging (MRI). However, this high resolution will be difficult to achieve in vivo because of dose limitations.

Due to the small-angle scatter rejection that the analyzer crystal can impose on the X-ray beam transmitted through the object, DEI has also a scatter loss or extinction contrast mechanism. This type of contrast is higher when images are taken near the peak of the rocking curve than the images acquired at either side of the peak when used for the DEI refraction angle analysis. This contrast mechanism is found to play a major role in the DEI contrast of fibrils in breast tissues [32]. In an apparent absorption image, microstructure information may be lost due to the decrease of the contrast caused by the small-angle scattering captured in the absorption image [34]. Algorithms to extract refraction angle images from DEI images have been developed and can further be improved especially for future phase-contrast X-ray CT applications [35–37].

Since multiple images with a variety of contrast mechanisms can be obtained by the DEI method, the multi-image radiography (MIR) technique has also been introduced [38,39], which shows an improvement over the conventional DEI. As in DEI, the MIR produces images that depict combined absorption and refraction properties of the object. However, the MIR produces a third image depicting the projected ultra-small-angle X-ray scattering property. This ultra-small-angle X-ray scattering comes from interactions of the probing wave field with fluctuations in the refractive index distribution on length scales that are small compared to the detector resolution [35,40], but much larger than the X-ray wavelength. To compute these images, the MIR reconstruction method requires knowledge of a collection of intensity measurements at different analyzer settings. In reported investigations of the MIR, the number of intensity measurements has been typically greater than five [38]. There remains, however, an important need to develop efficient data acquisition strategies and robust image reconstruction methods for the MIR [41].

**X-ray imaging by interferometer**

It is known that the phase of light revealed by optical interferometry may convey information on optical properties and/or geometrical features which cannot be accessed by simple intensity measurements. The early development of phase-contrast X-ray imaging techniques was indeed based on the use of X-ray interferometers, pioneered by Bonse and Hart in 1965 [42]. Along this direction, recent efforts have been made by Momose [43,44], Sutter et al. [45] and Takeda et al. [46] among others. The interferometry imaging is thought to be the most sensitive method for the phase-contrast X-ray imaging since the X-ray deflection due to refraction at the sample is detected as interference fringes and the fringe spacing is inversely proportional to the deflection angle, which is normally quite small in soft tissues. However, when the deflection is large, the X-ray interferometry method is not so suitable because these fringes may become too narrow to be resolved by standard imaging methods [47]. As a result, the interferometry method is considered to be most suitable for imaging structures in soft tissues without structural boundaries with
large difference in refractive indices, such as at tissue–air boundaries. Shown in Fig. 6 is an X-ray interferometer, called the triple Laue-type (LLL) interferometer, in which there are lamellae at regular intervals [42]. The first lamella (the splitter crystal) divides an incident monochromatic X-ray into two separate divergent coherent X-ray beams, which are inclined by the Bragg diffraction angle. The two beams are spatially separated at the centre lamella (the mirror crystal) and each is divided into two again. Among the four generated beams, the two convergent beams overlap coherently at the third lamella (the analyzer crystal). Each beam is again divided into two and interference occurs between the outgoing beams. This configuration corresponds to that of the Mach–Zehnder interferometer.

Although optical interferometers have been used widely, the construction of the X-ray interferometer is, in general, more complex. Since the wavelengths of X-rays are much shorter than visible light, much tighter alignment and greater mechanical stability of the components of the interferometers are required. As we know, in optics, the fluctuation of optical path length is the most sensitive factor in the interferometer design. When the path difference between the interfering X-ray beams fluctuates by more than one wavelength, the corresponding shift of generated interference fringes exceeds the spacing of the fringes. If the time required to record the fringes is longer than the time constant of this fluctuation, fringe contrast is lost. In order to observe interference fringes, an interferometer must be stabilized during the measurement to a level significantly finer than the X-ray wavelength. At present, the best results are so far obtained from a monolithic interferometer device, made from single large crystalline silicon ingot. Although this technique provides inherent alignment and good stability, the sizes of the single crystalline silicon ingot limit the potential field of view to about 5 cm × 5 cm. However, clinical applications such as mammography require, at least, a 10 cm × 10 cm field of view [48]. Another disadvantage of the monolithic LLL X-ray interferometer especially for imaging a living body is that the interferometer can be deformed by the heat radiated from the body, which is in close proximity to the crystal lamellae.

Since all interferometers need a coherent beam with sufficient flux, the sources available for the interferometry are limited. Recent development of synchrotron radiation X-ray sources has made it possible to use high X-ray fluxes with sufficient coherency, and technologies for fabricating and aligning various optical components for X-rays have been progressing. As a result of this, a variety of X-ray interferometers have been operated successfully and used for X-ray interferometry imaging. To overcome further the high stability requirement for an interferometer, short pulses of X-rays with high peak brilliance should preferably be used. Since the exposure time could be made much shorter than the period of crystal vibrations, the acquisition of a stop-motion picture of the fringes is possible. Therefore, a variety of X-ray interferometers can be operated without requiring extremely high stability by using, for instance, X-ray sources from third-generation synchrotron radiation facilities [49] and X-ray free-electron laser sources [50].

Furthermore, X-ray phase measurements can permit 3D imaging using a tomographic technique similar to the conventional X-ray CT [51]. Assuming that the phase map corresponds to a projection of the refractive index of a sample, the 3D distribution of the refractive index in the sample can be revealed by processing phase maps obtained by projection in multiple directions. Recently, Momose, Takeda and colleagues have incorporated the X-ray interferometer technique into computed tomography [46,47]. By taking several interferometry images at different rotational orientations of a sample, they are able to reconstruct a 3D map of the refractive index inside the sample. With this technique, they have studied the cerebellum of a rat and cancer lesions in a rabbit as well as cancerous tissues of human breast, liver and kidney by using the synchrotron radiation X-ray source at the Photon Factory in Tsukuba. Their results illustrate the potential advantages of phase-contrast and its sensitivity to minute density variations on the order of $10^{-9}$ g/cm$^3$ [48]. A spatial resolution of few microns may also be possible in phase-contrast X-ray CT of biological tissues [44].

**Differential phase-contrast X-ray imaging**

Interferometry and crystal analyzer-based imaging modalities rely on highly parallel and monochromatic X-ray beams due to the dependence on crystal optics. Although the inline phase-contrast method can overcome the stringent requirement on temporal coherence, it requires still the spatial coherence, which is currently only available from microfocus X-ray sources often associated with correspondingly low photon intensity or synchrotron radiation sources. An alternative method using grating-based differential phase-contrast (DPC) imaging has therefore been introduced recently, which may be used to retrieve quantitative phase-contrast images with polychromatic X-ray sources of low brilliance [52–55].

In the DPC set-up, shown in Fig. 7, there are a source grating $G_0$, a phase grating $G_1$, and an analyzer absorption grating $G_2$ with their respective periods $p_0$, $p_1$ and $p_2$. The source grating, typically an absorbing mask with transmitting slits, placed close to the X-ray tube anode, creates an array of individually coherent, but mutually incoherent sources. The ratio of the width of each line source to the period $p_0$ should be small enough to provide sufficient spatial coherence for the DPC image-formation process. As the source mask $G_0$ can contain a large number of individual apertures, each creating a sufficiently coherent virtual line
source, conventional polychromatic X-ray sources with sizes of more than a square millimetre can be used. To ensure that each line source produced by \( G_0 \) contributes constructively to the image-formation process, the geometry of the set-up should satisfy the condition: 
\[
p_0 = p_1/d,
\]
where \( l \) is the distance between the source grating and the phase grating, and \( d \) is the distance between the phase grating and the analyzer grating [55, 56].

The essential parts of the so-called Talbot interferometer used here in the DPC imaging are the two gratings, \( G_1 \) and \( G_2 \), placed between the object and the image detector, which act as an array of collimating slits that have a transmission depending strongly on the relative position of the two gratings and the angle of incidence. When the phase grating is illuminated by coherent X-rays, periodic patterns (self-images) are generated at specific distances from the grating, which is known as the Talbot effect [57]. If an object is placed in front of the grating, it deforms the self-images, depending on the differential phase shift caused by the sample object. In the Talbot interferometer, the deformation is depicted in an area detector as a moiré pattern, which is formed by the second grating (analyzer grating) placed on a self-image. Because the fringe spacings of the moiré patterns are much larger than the period of the grating, X-ray image detectors with a moderate spatial resolution can be used and are available. This is one of advantages of the DPC method since the use of X-ray detectors with moderate spatial resolution for high-resolution phase-contrast imaging may offer increased detection efficiency even at higher energies. Another advantage is due to the fact that the first derivative of the phase shift is measured in the DPC method in contrast to the in-line phase-contrast method, where the data contain essentially the second derivative of the phase shift, which makes the evaluation of noisy data more difficult.

In the DPC method, the differential phase shift by the sample can be quantitatively retrieved by a fringe scanning technique, which is performed by moving one of the gratings in the direction of its period. Phase tomography may also be obtained by repeating the measurement at plural angular positions of the object rotation. In this approach, any local phase gradient in the object causes a local change in intensity recorded by the detector, similar to diffraction-enhanced imaging. For a weakly absorbing object, the detected intensity is a direct measure of the local phase gradient of the object in this approach. The total phase shift of the object can thus be retrieved by a simple integration. A higher precision of the measurement can be achieved by splitting a single exposure into a set of images taken for different positions of the grating \( G_2 \) [58]. Thus, this approach allows the separation of the DPC signal from other contributions, such as non-negligible absorption in the object. Because the DPC image formation is not intrinsically coupled to the absorption of X-rays in the tissue medium, radiation dose may potentially be reduced by using higher energy X-rays. In comparison with the X-ray interferometry method discussed above, the DPC method does not require high mechanical stability and has the possibility of using detectors with large pixels and a large field of view since fabrication of large-area gratings is relatively easy nowadays by using standard photolithography and LIGA technique [56].

In a recent study [59], the DPC method has also been implemented by using a microfocus polychromatic X-ray tube, where the source grating \( G_0 \) is not required. In this case, the spatial coherence length of the system at the plan of the analyzer grating \( G_2 \) has to be made larger enough \((>m\lambda_0/4)\) so that interference pattern has a reasonable degree of modulation. Here, \( m \) is an odd integer, which corresponds to the order of the fractional Talbot distance. The cone beam set-up of such a DPC system has an advantage of being able to magnify the image at the detection plane. Thus, high-resolution phase-contrast images in the micron range may be obtained with a detector of moderate resolution. It was shown both theoretically and experimentally that the primary measurement signal and the differential phase shift determined are lowered as the magnification is increased. This effect can be compensated by enlarging the distance between the phase grating and the analyzer grating according to the authors.

Some limitations may exist also for the DPC method, as commented recently by Olivo and Speller [60]. The grating parallel apertures longer along the X-ray propagation direction than in the transverse one in this method may lead to a limited angular acceptance and therefore a substantial exposure time increase with non-parallel beams. Two gratings placed downstream of the sample may also result in inefficient dose delivery, which is important in medical applications. Further efforts in improving the present version of the DPC method are therefore encouraged.

**Potential medical applications of phase-contrast X-ray imaging systems**

The use of X-rays for medical purposes started almost immediately after Röntgen’s discovery of X-rays in 1895, and the first clinical X-ray images were done in 1896 and so was the first radiation treatment. Since then the use of X-rays has probably been the most important diagnostic imaging method. At present, clinically used X-ray imaging systems are essentially based on attenuation-contrast X-ray imaging techniques with the use of polychromatic X-ray sources. However, conventional attenuation-based X-ray imaging systems have not been so successful in differentiating various soft biological tissues due to the weak absorption-contrast, in spite of the great efforts that have been devoted to the fruitful development of X-ray...
imaging technologies, including X-ray CT systems during the last decades.

More recently, the technological advancement of synchrotron radiation sources [61, 62] as well as new compact X-ray sources with high brightness, such as the liquid-metal-jet anode electron-impact X-ray sources [63, 64], the plasma-based X-ray lasers [65–67], and the quasi-monochromatic tunable inverse Compton scattering X-ray sources [68, 69], has made it possible to implement practical phase-contrast imaging. These new approaches have excellent capability to improve soft biological tissue contrast over conventional attenuation-based X-ray imaging techniques in many clinical applications. In this section, some of potential medical applications of the phase-contrast X-ray imaging techniques are discussed.

**Phase-contrast X-ray angiography**

X-ray angiography is an important medical imaging technique to visualize blood vessels and their associated structures [70]. For instance, coronary artery angiography is an important clinical technique, which provides detailed high-resolution images of the vascular tree of the heart. In conventional coronary angiography, a catheter is inserted into the iliac artery and guided through the aorta and to the beginning of coronary arteries. An iodine-containing contrast agent is injected into the artery and radiographs are then taken at short intervals. If the stenosis is not too severe, the coronary angiography is followed by balloontipped angioplasty [71]. The method is well developed, but still complications and even mortality are too frequent to allow conventional coronary angiography to be used as a routine diagnostic method for screening or follow-up studies. Attempts to avoid the risks by intravenous injection of the contrast agent may, however, fail since, by the time the bolus reaches the coronary arteries, it is usually diluted to a few percent of the initial concentration. The use of heavy element contrast agents may also cause allergic reactions and vascular damage in some patients.

Recently, phase-contrast X-ray imaging techniques have been tested for angiography applications. It turns out that this new X-ray imaging technique may offer improved opportunities in angiography due to its excellent contrast for soft tissue imaging. Although, for some vascular systems of clinical interest, contrast agents may still be required also for phase-contrast X-ray imaging, new types of contrast agents without heavy elements may be introduced to reduce some of the negative effects, such as allergic reactions. Experimentally it has been demonstrated by using the technique of the phase shift X-ray interferometry for blood vessel imaging [72, 73]. It was shown that vessels of the rat liver filled with physiological saline (having a relatively low refractive index in comparison with that of normal liver tissue) are clearly revealed in the phase-contrast X-ray image, whereas the corresponding attenuation-contrast X-ray image could not resolve the vascular structure. In particular, vessels of about 30 μm in diameter with physiological saline are revealed clearly in the phase-contrast X-ray image. Readers, who are interested in these images, are referred to the original article [73]. Without contrast agents, blood vessels with a diameter of about 50 μm have also been detected by using the phase-contrast X-ray interferometer method [72]. Conversely, the attenuation-contrast X-ray image with iodine-loaded acrylic microspheres demonstrated only large vessels of 100 μm in diameter at almost the same X-ray dose. In these studies, the phase-contrast X-ray images were obtained by using a monochromatic X-ray beam with photon energy of 17.7 keV at a synchrotron X-ray facility, and a monolithic X-ray interferometer having a 25 mm × 25 mm field of view, made from a perfect single-crystal silicon ingot.

It is expected that with higher X-ray energy, it is possible to image blood vessels in thick objects of soft tissues using phase-contrast techniques. If a sufficiently high-flux-density X-ray beam is available, it is also possible to make dynamic phase-contrast X-ray imaging of blood flow conditions in blood vessel structures of clinical interest, such as those in tumours since a hypoxic tumour stimulates the creation of new blood vessels for improved oxygen and nutritional supply. Here, in comparison with other imaging modalities, the phase-contrast X-ray imaging method may offer extremely high-resolution images that are required to visualize blood capillaries. Such a study could also be potentially useful for investigating blood flow conditions helpful in understanding drug delivery mechanisms among others. At present, X-ray beams with extremely high flux density are only available at large synchrotron radiation-based X-ray facilities [49].

**Cartilage bone and cancellous bone imaging**

Non-invasively detection of cartilage abnormalities is important to discover initial stages and early progression of degenerative joint disease or osteoarthritis [74]. At present, osteoarthritis is a prevalent and poorly understood disease that affects the cartilage and other tissues in the joints of aging people, having a serious impact on the quality of life. Information on the structure of normal cartilage and the ways in which this tissue, with limited or no ability to repair, changes after damage or disease is essential for the development of rational treatment strategies. However, conventional attenuation-based contrast radiology is sensitive only in the case of advanced disease in which there has been a loss of cartilage. Other alternative imaging methods, such as magnetic resonance imaging and ultrasound, have generally poorer spatial resolution than X-rays.

With the use of phase-contrast X-ray imaging, it is now possible to visualize cartilage and detect early degenerative changes. For instance, by using the DEI X-ray imaging technique with a synchrotron radiation source, human articular cartilage is not only visible, but also gross cartilage defects, even at early stages of development, can be visualized due to the combination of high spatial resolution and detection of X-ray refraction, extinction and absorption patterns in the DEI images [75, 76].

The DEI technique is also capable of rendering high-contrast images of bone and can be used to visualize the edges of cortical and cancellous bone. The refractive properties of spongy or cancellous bone architecture may then provide a 3D architectural appearance: a feature that is lost in conventional radiography. In Fig. 8, two synchrotron X-ray images are shown for a knee joint of a New
Zealand white rabbit [77]. Fig. 8(a) shows the synchrotron radiograph taken at 30 keV without the analyzer crystal in place, which is a typical non-DEI radiograph of the rabbit knee joint. Fig. 8(b) shows the diffraction-enhanced refractive image of the same sample. It can be seen from Fig. 8(b) that the delineation between cortical and cancellous bone is more clearly seen, and the cancellous trabeculae have a 3D appearance owing to the refraction information gleaned through diffraction-enhanced imaging with the X-ray intensity set at the shoulder of the rocking curve. The results indicate that DEI is capable of rendering high-contrast radiographic images of bone owing to its ability to reject scatter and enhance edges. Similarly, by using a synchrotron source, small fractures in bone invisible by conventional techniques may also be detected by an in-line phase-contrast X-ray imaging technique [78].

Renal and prostate carcinoma imaging

By using highly collimated synchrotron hard X-ray beams at the Pohang light source and the in-line phase-contrast X-ray imaging technique with unmonochromatized X-rays, refractive index radiographic images of two common urological malignancies, renal cell carcinoma and prostate adenocarcinoma in a specimen of 3 mm thickness were obtained by Yoon et al. [79]. The images were compared with those of optical microscopy to determine anatomical features. In their system set-up, transmitted X-rays are captured by a thin (200 μm) CdWO₄ double-polished single-crystal scintillator and converted to a visible image. The image is then magnified by an optical lens before being captured and stored by a CCD camera (typically 1600 pixels × 1200 pixels). The spatial resolution of the imaging system reaches about 1 μm. It was shown that small organelles in normal renal cortex such as glomeruli and surrounding proximal tubules are well identified in the phase-contrast image with close similarity to that of low-magnification optical microscopy [79]. However, more glomeruli are visible in the radiographic images than in the corresponding microscopic images at similar magnifications. The tubules around the glomeruli also seem to be more densely packed in the radiographic image. According to the authors, these fine features may be due to the projection of multi-layered cells and organelles in a single image since the hard X-rays can get image information from deeper layers inside the tissue sample than that conventional histological microscopy.

Phase-contrast images of renal cell carcinoma were also obtained in their work, demonstrating the characteristic features of whirl-like structures in the central area of a tumour next to a peripheral portion with filicoid branching pattern. Similarly findings have been made using optical microscopy. Benign histological features of a human prostate, such as normal gland, smooth muscle components, and benign adenoma with optical microscopic details were also visualized successfully by using the in-line phase-contrast X-ray imaging technique. A tiny tumour (less than 5 mm in diameter) was discriminated without difficulty. Readers of interest are referred to the original article [79].

Lung imaging

Conventional attenuation-based radiography has had limited success in detecting lung diseases, in which the variation in tissue density created by a pathological process is often too small to be detected, especially for early stage lung diseases. Even in their more advanced stages some diseases, particularly interstitial lung disease can show completely normal chest radiographs [80,81]. However, since a significant degree of X-ray phase-contrast can be created at the air–tissue interfaces in lung, it is possible to make use of the phase-contrast imaging techniques to image lungs for improved lung diagnostics. Indeed, efforts have been made recently to image lungs of mice and live rabbit pups with both the in-line phase-contrast imaging method and the DEI method [82,83].
In Fig. 9(a), the conventional radiograph of an adult mouse is shown, using a Siemens Nova 3000 conventional mammography system at 26 kVp at a surface dose of about 1 mGy \[82\]. High-contrast is noticeable between bone and soft tissues. However, the contrast between soft tissues is very weak and difficult to distinguish. No obvious lung structure is visible. Fig. 9(b) and (c) show the phase-contrast images of a 1-month-old male mouse from, respectively, the in-line phase-contrast imaging method and the DEI method at 33 keV. The surface entrance doses received by the mouse are, respectively, 8.6 mGy for the in-line phase-contrast method and 0.91 mGy for the DEI method. It is shown that with the phase-contrast, the lung tissue clearly stands out from surrounding soft tissues, where the improved visibility of the lung results from the speckled intensity pattern. The authors anticipate that analysis of the speckled intensity patterns seen with phase-contrast images may potentially assist in determination of lung tissue diseases, which requires further exploration \[82\]. Study of dynamic phase-contrast X-ray imaging of lungs indicates further that the phase-contrast X-ray imaging technique may identify and locate airway liquid and allows lung aeration in newborn rabbit pups to be dynamically visualized \[83\].

### High-contrast mammography

Nowadays, breast cancer is one of the dominating causes of death of women in industrialized countries. Although very early detection of breast cancer may lead to almost 100% successful therapy, practical use of mammography for systematic screening of breast cancer \[84\] has so far been quite limited due to the weak attenuation contrast of conventional X-ray imaging techniques in differentiating soft tissues, especially normal and abnormal breast tissues at small scales, where the elemental composition is almost uniform and the density variations are small. Recently, phase-contrast imaging techniques have been developed rapidly to visualize microstructures of soft biological tissues under low radiation dose \[11\], among which the DEI technique whose contrast may come from the absorption, the refractive gradient, and the small-angle scattering rejection (also called extinction) has been studied extensively for mammography applications \[85–89\].

Early in 1998, by using a sealed X-ray tube with an Ag water-cooled anode and a fine focal spot size of \(0.23 \text{ mm} \times 0.4 \text{ mm}\), a diffraction-enhanced phase-contrast X-ray imaging technique was introduced to image breast tissues by Ingal et al. \[90\]. It was shown in their work that phase-contrast images with a 22.2 keV monochromatic X-ray beam could reveal the changes in parenchyma structure due to malignancy and microcalcifications down to 50 \(\mu\)m in size. Their results were verified by histological examination. Since microcalcifications of about 100 \(\mu\)m are critical objects in the breast tissue that may provide an indication for breast cancer, a high spatial resolution with the mammography system is therefore mandatory. Due to the dramatic contrast enhancement and resolution increase by phase-contrast imaging, the use of digital detectors of high quantum efficiency may provide a dose reduction factor of 5–10 in future phase-contrast mammography screening systems.

Recently, using synchrotron radiation sources, the DEI imaging technique has been adopted to investigate refraction angle contrast mechanisms and its apparent absorption images, as well as correlation with conventional attenuation-based contrast radiography \[32,86,89\]. It was shown that the DEI refraction angle contrast and radiograph contrast both depend on the density difference between the two materials (fibrils and normal tissue) since they are based on the same physical mechanism, namely the increased density of cancerous fibril tissue. However, the refraction angle depends on the gradient of the thickness. This property of the refraction angle image makes it very sensitive to the edges of imbedded objects while the absorption image is most sensitive to the thick region of the object. This complimentary behaviour of the refraction angle image and the absorption image is an advantage of the DEI technique in determining the boundaries of cancerous tissues. Furthermore, it was observed that the contrast of...
the DEI apparent absorption image far exceeds that of the conventional absorption image due to the presence of an additional contrast mechanism, the extinction, which comes from the scatter rejection that the crystal analyzer imposes on the X-ray beam transmitted through the object. It was shown by Hasnah et al. [32] that the apparent absorption image of a breast tissue sample with invasive lobular carcinoma has significantly higher contrast than expected by conventional radiography.

By taking into account multiple contrast mechanisms (absorption, refraction, scattering), future X-ray imaging modalities may lead to further improvements in system performance in future generations of multi-contrast mammography, besides the possibility of introducing phase-contrast CT techniques for improved 3D imaging. Interestingly, some efforts have already been made recently to test the phase-contrast mammography for patients in Italy, based on the synchrotron radiation clinical mammography [91], as well as by the phase-contrast mammography system developed at Konica Minolta Medical & Graphic, Inc. [23].

3D phase-contrast X-ray imaging

Like conventional radiography, phase-contrast X-ray imaging techniques offer projected 2D images on which tissue structures can be visualized. However, since the projection of 3D anatomic information onto 2D image will complicate subtle difference in X-ray transmission and objects at different depths will be superimposed on each other, the subtle difference in subject attenuation, diffraction and contrast may not be clearly visible or completely lost. This will also be the case for phase-contrast X-ray imaging. However, this problem can largely be eliminated by the introduction of computed tomography, which has in fact revolutionized diagnostic X-ray imaging by allowing full 3D or 4D anatomy to be imaged in transverse layers. Its superior visualization of subject contrast, together with depth localization and display of anatomy across planes that are not accessible by conventional imaging techniques have made the X-ray CT exceptionally useful for visualizing anatomy in the living body. Today, with the aid of array detector technology introduced in the 1990s, the X-ray CT allows imaging of whole organs in a fraction of a second or the whole body in just 5–20 s with sub-millimetre almost isotropic resolution [51]. By introducing phase-contrast in CT imaging, significant performance improvements may be anticipated in upcoming CT systems for medical application, even though there are still many technological challenges to be solved before it reaches the hospitals.

X-ray phase measurements permit 3D imaging using both tomographic and stereoscopic techniques. The large amount of extra information in a projected phase-contrast image (cf., Figs. 8, 9, and 11) will, as mentioned, make it very difficult to interpret a single projected image of a thick complex object, as seen in the lower panel of Fig. 9. However, by always registering a stereoscopic pair of images, the different phase-contrast signatures cannot only be separated in their x- and y-axis projections but also along a depth axis z, using a stereoscopic readout system. With ordinary attenuation contrast, stereoscopic imaging was never very popular since the contrast was too weak and it was difficult to get a good 3D impression as the structures forming the 3D image contained very little information. This situation is reversed with phase-contrast imaging since the high amount of image information and structure can now be used to significantly improve the 3D visibility of phase-contrast objects simply by stereoscopic imaging. So even if each projected image of a stereoscopic pair is hard to interpret on its own, the high amount of phase-contrast structures makes them clearly distinguishable in 3D stereoscopic view. This opens up the field of 3D phase-contrast imaging to low-dose imaging with only two planar projections instead of more than 300 images needed for good CT reconstruction. Obviously the exposure time for each of the CT projections need not to be as long as for each of the images of the stereoscopic pair. However, there may still be a substantial saving in patient exposure at the same time as it is not necessary to rotate the X-ray source around the patient or to rotate the patient. The stereoscopic phase-contrast technique is therefore suitable for use with many of the new generation of advanced X-ray sources that are almost impossible to rotate, such as synchrotrons, wigglers, undulators, monochromators, X-ray free-electron lasers, inverse Compton X-rays, and liquid-metal-jet targets. Of course, one can rotate the patient. However, this is not desirable from a clinical point of view since it may cause undesirable complications due to tissue and organ motions, especially for the relatively high rotational rates needed for freezing organ motion, such as breathing and heart beat. Furthermore, rotating a patient will make it difficult to implement some on-line image-guided therapeutic interventions, such as the image-guided biopsy, surgery and even radiation therapy.

By using the stereoscopic technique, not only can the stereoscopic pair be generated by only a small rotation of the object or beam and detector or using two separate imaging channels, but it will also reduce the exposure time significantly, including substantial reduction of the 3D imaging time. With the use of two simultaneous imaging channels, it will even be possible to do instantaneous imaging, freezing organ motion down to milliseconds and even faster. This can be especially desirable in the thorax region with heart beat and breathing motions that otherwise may blur and even remove a substantial part of the new phase-contrast information. We can therefore expect an interesting development of fast stereoscopic phase-contrast X-ray imaging for accurate high-resolution 3D visualization in the coming years.

Fig. 10 shows an example of a possible stereoscopic phase-contrast X-ray system for 3D/4D medical imaging and cancer diagnostics on patients. Interestingly, this setup allows 3D imaging without the rotating systems used by CT-scanners and can thus be used with a stationary patient and any of the large modern high coherence X-ray sources. With the stereoscopic technique, it becomes possible to make 3D imaging with an exposure time of less than a tenth of a second and probably as low as a millisecond. With special X-ray tubes, it may even be possible to get X-ray pulses down to tens of nanoseconds [92]. Substantial improvements in thorax radiology are thus in reach with significantly higher resolution, higher contrast and faster imaging sequences. In fact, the new technique with stereoscopic phase-contrast imaging suggested here might be the only technique that
will make sub-micrometer to micrometer 3D imaging possible in man. This is because many of the internal motions, such as heart beat, breathing and peristaltic motions will blur the images. Thus, the high intrinsic resolution available with the very sharp X-ray sources that are generally used for phase-contrast imaging will largely be lost. With two short pulses of X-rays in stereoscopic configuration, all these motions can instead be frozen, particularly if the two pulses are simultaneous and short enough.

To improve the 3D alignment of identified tumour volumes, a laser camera for accurate 3D surface monitoring can be combined with the high phase-contrast information from the internal structures. Together the high 3D volumetric phase-contrast and 3D surface imaging laser camera will generate a well-defined 3D volume that can be precisely aligned with other imaging modalities like MR and PET-CT for accurate treatment planning. It may be suitable to include a 3D haptic interface to accurately localize the target volume in three dimensions. Here, one may also include a computer-based expert system to assist human brain-power and intelligence in analysing medical images and making diagnostic judgements. The expert system can be constantly updated during the course of both laboratory experiments and regular clinical applications, just like a radiologist gaining gradually his experience and skills in analysing the radiographic images to identify subtle lesions and/or cancer signatures. In the future, X-ray holography systems can be of interest for biomedical research. Holographic applications are very challenging and require further development of novel X-ray sources and detectors, as well as innovative holographic system concepts.

At the recent meeting of the Radiological Society of North America (2007), an interesting and encouraging finding was that a stereoscopic form of conventional mammography appears to be much more effective than standard film mammography in detecting subtle lesions, enabling mammographers to detect lesions that are not clearly visible on standard films. According to the investigation, the false positive cases in breast diagnosis were reduced from about 40 to 24 using stereoscopic mammography imaging with ordinary attenuation-based X-ray contrast. This corresponds to almost a 50% reduction of the false positive rate. This finding suggests that 3D viewing techniques will allow clinicians to detect more true lesions and could significantly reduce the number of women who are recalled for additional tests or even biopsy following routine screening mammography. While this positive result has been reported for ordinary stereomammography based on a conventional attenuation-contrast X-ray imaging system, we anticipate that, by further introducing stereoscopic phase-contrast X-ray imaging techniques, we may significantly improve the system performance at least another factor of two or even more with high-resolution imaging. Obviously, fast imaging will be essential here to freeze breathing and heart beat.

At present, algorithms for phase-contrast tomography have been developed to reconstruct a quantitative 3D map of the refractive index distribution. The filtered back-projection algorithm of conventional (absorption) CT has also been applied to reconstruct an image that contains information regarding the locations of edges or boundaries in the refractive index distribution. Experimentally the phase-contrast X-ray computed tomography (PCT) has been studied since 1990s by a number of research groups. In the work of Momose, it was shown that by using an X-ray interferometer and...
synchrotron radiation source, the PCT image could be obtained by converting an interference pattern into an image of phase shift distribution, which was then put into a CT algorithm. For a test object of a plastic sphere, PCT images with a spatial resolution below 40 μm was demonstrated [43]. The signal-to-noise ratio (SNR) for the PCT imaging is increased by about 10 times over that for ordinary attenuation-contrast X-ray CT imaging. Similarly, by the phase-contrast X-ray CT, the 3D imaging result for a non-stained sample of a cancerous rabbit liver indicated clearly its capability of differentiating the cancer lesion from the normal tissue, including ability to depict fine structures corresponding to cancerous degeneration and fibrous tissues [103]. The interferometer-based PCT has also been used to image colon cancer specimens, results of which are then compared with those from MRI and optical microscopy [46]. It was shown that the interferometer-based phase-contrast X-ray CT image taken at 35 keV X-ray energy can reveal clearly the inner structures of the colon cancer masses, such as cancer, necrosis, surrounding tumour vessels and skin in a similar way to the low-magnification optical microscopy images. With approximately fourfold higher SNR than MRI, the PCT may also exhibit higher image quality than the MRI (at 4.74 T) image for formalin-fixed biological samples and was thought to be suitable for detailed imaging of soft tissue with high volumetric resolution [46]. Further efforts for in vivo imaging are, however, needed to properly evaluate image qualities between the PCT and MRI methods. By the PCT, 3D image of the colon cancer specimen was also obtained [46], which can be useful for quantitative analysis of pathological structures of cancerous specimens.

Recently, X-ray CT techniques have been investigated to improve image qualities in conventional mammography in order to localize and classify tumours. Due to its improved SNR and reduced structural artefacts without breast compression, the performance of the breast CT in early breast cancer detection is likely to be quite impressive. In a recent study [110–112], it was shown that lesions as small as 2 or 3 mm in diameter may be easily detected by breast CT compared to a median lesion diameter of 11–16 mm detectable by screen-film mammography. Thus, much earlier detection is possible with the breast CT, which is of importance for reducing the morbidity and mortality of breast cancer. At present, the resolution and contrast of the clinical whole-body CT have not yet been sufficient to reveal subtle morphological features that are the signature of malignant breast tumours. It is expected that the use of phase-contrast X-ray imaging techniques in CT may remove many of the limitations that current diagnostic X-ray mammography suffers.

The diffraction-enhanced X-ray imaging technique (DEI-CT) has been studied for breast cancer imaging [37,87,106]. Due to different contrast mechanisms, mammograms obtained with DEI appear quite different and complex in comparison with conventional attenuation-based images. It is not straightforward to interpret DEI images, and in particular, to identify malignant lesions and differentiate them from normal tissues. Some efforts have been made to facilitate interpretation of the DEI-CT images through comparison with conventional images and histology of the samples [105]. The significance of the DEI-CT for mammography will depend on the capacity for finding signatures for breast cancer not visible by other methods and on improving the sensitivity and specificity of the radiological examination. In a recent study of the DEI-CT technique by Bravin et al. [37], using a synchrotron radiation source (33 keV monochromatic X-ray) and a high-resolution CCD detector (with an effective pixel size of $47 \times 47 \mu m^2$), high-resolution DEI-CT images were obtained, in which large contrast enhancement was achieved, permitting visualization of details that generally are invisible in clinical radiographs.

Shown in Fig. 11 are some images obtained for a tissue sample with ductal partly lobular carcinoma [37]. In the histological section shown in Fig. 11(a), in situ carcinoma and microcalcifications are seen in the upper quadrant on the right side of the specimen. The indicated collagen septum is normal and includes nerve crossings, ducts, liponecrosis and elastosis. The dark area below the centre of the specimen contains a large number of microcalcifications. According to the radiologist, the mammogram (Fig. 11(b)) indicates suspicious malignancy. The clinical CT image (Fig. 11(c)) does not suggest any abnormality, and even the thick collagen strand on the right side of the specimen looks normal. The DEI-CT TOP image (Fig. 11(d)) shows, however, abundant details, which correspond to the structures of the histological section. The TOP image reveals best the concentrations of microcalcifications (arrowheads) in the suspect areas as confirmed by the pathologist, and also near the stem of the thick collagen septum on the right side of the specimen. Thus, in comparison with optical images of stained histological sections with three malignant and benign samples, these authors were able to show that DEI-CT images accurately map the morphology of the samples, including collagen strands and microcalcifications of dimensions less than 0.1 mm. However, clinical attenuation-based X-ray CT images were shown to suffer from insufficient spatial resolution. Although the collagen-rich areas are visible in the attenuation-based CT image, their inner structures are washed out in the image and collagen strands in the adipose tissue cannot be discerned. The combination of synchrotron-based DEI and DEI-CT has so far made images of breast tumours that are extraordinarily similar to pathological histology [37,106].

**Challenges, system prospects and potential developments**

X-ray imaging techniques based on the phase-contrast mechanism may offer greatly enhanced image quality over conventional attenuation-based imaging techniques, as demonstrated recently in synchrotron laboratories by a number of research groups. Like most of new technologies, the clinical introduction of the new phase-contrast X-ray imaging modality will be a challenging task. First of all, X-rays are known to be an ionizing radiation, which may cause damage to living tissues. For diagnostic radiography applications, especially mammography screening, the X-ray doses have to be very carefully controlled and maximum limits have to be set to minimize the risk for the patient. The limits set are normally well below doses that may harm. However, although quite safe, there is always a slight risk of long-term secondary cancer induction.
Encouragingly, recent studies on breast tissue specimens have demonstrated superior quality of phase-contrast X-ray images at either similar or lower doses than used in conventional mammography [6,11,111,112]. For instance, a factor of about 10 for the contrast improvement offered by the DEI technique was reported [113], compared with conventional attenuation-contrast images at the same dose. Efforts may further be made to reduce the dose while keeping high quality images by optimising, for instance, X-ray photon energy and its useful energy band for the phase-contrast imaging in specific clinical settings. Equally important is the optimisation of system design with the aid of novel X-ray sources and high-performance cost-effective detectors with high DQE, including the design of the imaging system depending on the specific phase-contrast imaging technique utilized.

While phase-contrast X-ray imaging can be very sensitive, it may also lead to difficulties. For instance, fine surface features may obscure internal structures. Thus, techniques have to be developed to reduce the potential for confusion of overlapping structures in planar images [6]. Reconstruction of volume images from 2D images of closely spaced slices from, for instance, the DEI-CT will need to be developed with the goal of producing high-resolution 3D images of tumours (that can be arbitrarily rotated on the computer screen) for accurate visual inspection [34]. For medical applications, further efforts are also required to establish a knowledge base for image interpretation so that details visualized in the phase-contrast images can be assigned easily to known lesions. In fact, although phase-contrast images provide an improved contrast over attenuation-based images for soft tissues, their interpretation remains a challenge since practically no clinical experience has so far been available on how tumour characteristics and structures are represented in such phase-contrast images in human.

Furthermore, for clinical imaging of live patients, effects of live tissue/organ motions on image quality are of particular concern. This is because many of the internal motions, such as heart beat, breathing and peristaltic motions will blur the images. Thus, the high resolution intrinsically available with the phase-contrast imaging may largely be lost. At present, the heart with as many as 1–3 beats per second is not easy to freeze even with today’s fastest CT scanner with about 3 revolutions per second. Innovative system concepts and methods to achieve fast high-resolution stereoscopic phase-contrast imaging are therefore required together with relevant component developments.

In general, high-resolution imaging systems based on phase-contrast X-ray imaging techniques require good mechanical stability for clinical applications. In some cases, extremely high stability is needed, for example, when using interferometry methods based on crystal optics. Monochromaticity is also an important issue for both DEI and interferometry techniques, in which monochromatic X-ray images are used.

**Figure 11**  (a) Image of a histologic whole-mount slide from the centre plane of 28 mm thick sample with ductal partly lobular carcinoma (Herovici’s stain; original magnification); (b) clinical screen-film mammogram of the same sample (26 kV, 8.0 mAs); (c) clinical CT image of the same sample (80 kVp, 50 mAs); (d) DEI X-ray imaging computed tomography (DEI-CT) TOP image of the same sample (33 keV) [37] (courtesy of Bravin A., reproduced with permission of IOP Publishing Ltd., Bristol).
beams with sufficiently high flux to record an image at a clinically realistic timescale are currently restricted to synchrotron radiation sources. Obviously it would be impractical to have advanced diagnostic systems located solely at major synchrotron radiation facilities. Although an in-line phase-contrast X-ray imaging technique does not require monochromatic X-ray beams, it does need an X-ray beam of sufficiently high spatial coherence if high-resolution images from diffractive effects of X-rays in the object could be explored. Conventional X-ray sources do not, however, provide such a collimated beam of high spatial coherence. Generation of X-rays with increased coherence with a pinhole technique is quite wasteful: of all the emission, only a few percent of the X-rays going through the pinhole is used. This implies that the practical flux intensity achieved with a collimated beam of high spatial coherence is limited, and so are its possible applications. The combination of small focal spot size and high flux remains a major technical challenge for X-ray source manufacturers.

The good news is the promising progress in the development of novel X-ray sources with high brightness. Recently, a high brightness (more than 100 times higher than conventional rotating-anode X-ray source) microfocus X-ray source has been demonstrated based on the liquid-metal-jet anode electron impact technique [63,64]. A compact quasi-monochromatic tunable inverse Compton scattering X-ray source of high-flux has also been demonstrated by the use of a laser and a linear electron accelerator technique [68,69] and its potential medical applications have been explored [114,115]. A compact (table-top) synchrotron X-ray source with high brightness (more than 1000 times higher than conventional X-ray tubes) has also been reported [116]. These new compact X-ray sources may have significant impact on future development of the phase-contrast X-ray imaging system for clinical applications. On the other hand, efforts are also being made in developing the next generation synchrotron radiation sources [49] as well as X-ray free-electron lasers (XFEL) [50,117]. These synchrotron radiation sources and XFEL are expected to have huge impact on basic scientific researches in revealing biological world at molecular scale in real time, but limited clinical usage due to their huge sizes.

From system performance point of view, besides X-ray sources, X-ray detectors play also an increasing role in improving image quality and fulfilling stringent requirements for medical applications, especially when dynamic imaging modalities are required like in 4D X-ray imaging [118]. Currently there is an increased use of digital imaging systems for clinical applications [119,120], which has advantages of being able to optimize image acquisition, display, storage and transmission separately, and, once the image information is recorded, one may allow arbitrary settings of image brightness and contrast without the need for further exposure to the patient by using computed image-processing techniques. In particular, new imaging systems based on multi-contrast mechanisms could only be realized in a digital imaging system.

Recently, much effort has been made to develop cost-effective high-performance digital X-ray detectors, for which the detective quantum efficiency is an important characteristic parameter [121]. The DQE characterizes not only the ability of a detector to transfer the information it receives at its input to its output, but also effectively the combined effect of noise and contrast performance of the digital X-ray detector. A digital detection system rendering high levels of contrast will not produce diagnostically useful images if its images are very noisy. On the other hand, the diagnostic utility of a system with very low noise will be equally limited if it is unable to render adequate contrast. Thus, both low noise and high-contrast performance are required for superior image quality and object detectability. Maximizing DQE at all spatial frequencies is therefore an important goal for future digital detector-based imaging systems.

In phase-contrast X-ray imaging, the diffraction and refraction fringes may enhance image quality only if they are visible. This requires both a proper X-ray source, such as a microfocus X-ray source, and a detector with sufficiently high resolution or suitably large imaging distances for image magnification without significant geometrical blurring. Whether phase or attenuation contrast is used for imaging, the resolution attainable in the image is obviously limited by both the source and the detector. The resolution is typically of the order of tens of microns for CCDs and scintillator-film systems [122,123]. To achieve sub-micron image resolution, large distances or some kind of X-ray optics, such as zone plates, curved mirrors or refractive lenses can be used to obtain magnification from a simple point source projection or the optic is implemented in a microscope configuration. Indeed, in the soft X-ray region (0.1—1 keV), a zone plate-based transmission X-ray microscopy has achieved a spatial resolution of 15 nm [124]. In the hard X-ray region, because of the difficulty in fabricating the required zone plates, such spatial resolution is not yet attainable, and values of around 60 nm are more typical [125]. For dynamic imaging, a high temporal resolution of the detector is also of importance. When the spatial resolution is increased, the radiation dose will also increase dramatically due to the increasing X-ray photon flux required in order to have a sufficient number of photons to avoid or reduce noise in detected images [126]. Thus, for clinical applications, a proper balance between the increased dose detriment and the increased image quality and resolution has to be found in the system design. Almost an order of magnitude in image resolution, compared with conventional attenuation-based X-ray imaging modalities, might be in reach at a similar dose level due to the increased phase-contrast and proper selection of the diagnostic photon energy, X-ray source and detector (cf. Fig. 1). Depending on applications, a perfect imaging modality would need detectors that can produce images with high spatial, contrast and temporal resolutions at an acceptable dose level. Some discussion about X-ray detectors for digital radiography has been given in the literature [127,128].

To improve further image contrast in soft tissues by phase-contrast X-ray imaging techniques, novel phase-contrast agents without using heavy elements may be introduced and tested in clinical environments. Interestingly it has been reported that acoustic radiation pressure may also be utilized as a kind of "phase-contrast agent", which is based on the fact that local change in tissue density may result in change in its refractive index [129,130].
Because Young’s modulus and mass density of a tumour are usually quite different from its surrounding tissues, the responses of the tumour and surrounding tissues to the acoustic radiation pressure are therefore different. Thus, a subtractive phase-contrast imaging method may be helpful to detect tumours, in which the phase-contrast in an image is enhanced by recording two consecutive images of an object. In the first image, the object is displaced slightly through acoustic radiation pressure, and in the second, the object is unaffected. By subtraction of the two images, motion-induced phase-contrast is obtained. The potential of this method was demonstrated by imaging microscopic tumour phantoms embedded into tissue with a thickness typically presented in mammography [129]. It is anticipated that this method may be used for the detection of small-size tumours and other lesions distinguished from surrounding tissues by their elastic properties and density differences as small as a few percent [129].

To summarize, by introducing the phase-contrast mechanism and with the help of recent technological developments in novel X-ray sources and detectors as well as digital system innovations, future generations of X-ray imaging systems may offer us great system performance improvement, especially for medical imaging applications with low dose and high quality, including 3D and/or 4D techniques not least for cancer imaging. In particular, phase-contrast X-ray tomosynthesis techniques [131] and stereomammography [132,133] based on the increased phase-contrast mechanism may be developed for cancer imaging to produce 3D digital images of high quality with low dose, besides the phase-contrast X-ray CT technique.

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References


