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X-ray Phase-Contrast Mammography

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51.1 Introduction

51.1.1 Background

Breast cancer is a major cause of female morbidity and mortality in industrialized countries. Its distribution and the economic burden it imposes on national health services make it a major public health concern. Worldwide, about 1.7 million new cases occurred in the year 2012, which corresponded to 25% of all cancers among women and over 0.5 million deaths due to breast cancer (IARC 2016).

Early diagnosis is a crucial factor in reducing breast cancer mortality. The diagnostic method, in general, should have high specificity and sensitivity, be as non-invasive and harmless as possible, and should take into account the limited financial, personnel, and time resources of the healthcare system. Today, breast cancer diagnosis is made by triple diagnosis; by physical examination, breast imaging, and fine-needle aspiration cytology or core needle biopsy. Mammography, where the radiographic contrast is due to absorption of X-rays, is the most broadly used and the only evidence-based breast imaging method for mortality reduction (Tabár et al. 2011) (see Section II, Chapter 19). Mammography is the morphological method enabling examination of the breast in its entirety and offering the highest sensitivity also for early-stage tumors. The specificity of X-ray absorption contrast mammography is strongly affected by breast density and reporting technique.

51.1.2 Screening Mammography

For breast cancer survival, the time of diagnosis is extremely important, since tumor size and stage at diagnosis are the most important prognostic indicators (Michaelson et al. 2002).
Finland was the first country to introduce nationwide breast cancer screening as a public health policy in 1987, and in 2003 the European Council recommended the implementation of population-based breast cancer screening programs (Hakama et al. 1997; European Union 2003). The favorable effects of organized screening are well established, and participants in organized screening programs, where 50- to 69-year-old women are invited to undergo mammography at 2-year intervals, are about 30% less likely to die from breast cancer (Vainio and Bianchini 2002; Fletcher and Elmore 2003).

Different incidence, mortality, and survival rates are due to differing risk factors, availability of organized screening programs, and access to effective treatment (Althuis et al. 2005; Berry et al. 2005). The mean European age- and area-standardized 5-year relative survival of women diagnosed with breast cancer in 1995 to 1999 was 79%, while 20 years later in Finland it was 91% (Sant et al. 2009; Ferlay et al. 2013; Finnish Cancer Registry 2016). However, the prognosis varies widely depending on stage, grade, and size of the primary tumor, with axillary lymph node involvement being of particular importance. In the choice of therapeutic approach, particularly when considering breast-conserving procedures, good diagnostic radiology methods are eminently important.

### 51.1.3 Diagnostic Mammography

Diagnostic X-ray mammography is an additional examination required when there are clinically suspect findings. It is used for differentiation of malignancies from benign breast diseases as well as their localization, classification, and extent evaluation. In this role the use of mammography is less efficient than in screening, mainly due to its limited specificity. Many benign and malignant lesions have considerable overlap in their morphologic characteristics in mammograms, so that the specificity is not enough to obviate the need for breast biopsy. Albeit mammograms are evaluated by experienced professionals, confirmation of diagnosis by triple diagnosis is always required in the presence of a suspicious sign or finding. Over recent decades experience has led to standardized recommendations for interpreting and reporting abnormal findings in mammograms. The most common signs of abnormalities encountered in mammograms are masses and calcifications whose radiographic appearances provide important clues to their etiology.

In X-ray absorption contrast mammography, almost all cancers will be apparent in fatty breasts. Radiolucent adipose tissue provides an excellent background for detecting even small abnormalities, which in most cases are dense in their radiographic appearance (see Section II, Chapter 28). Mammography can also provide excellent visibility of calcifications, which are present in 45% to 65% of breast malignancies and in about 20% of benign diseases (Berg et al. 2001). However, the major challenge of mammography comes with the detection of cancer, particularly in pre-menopausal women with predominantly dense breasts: only half of tumors are visible in extremely dense breasts (Roubidoux et al. 2004). This results, in large part, from the masking or camouflaging of non-calcified tumors by surrounding dense tissue. Various studies have reported overall sensitivities of 80% to 90% for mammography, but as the sensitivity is inversely proportional to the breast density it declines down to 30% in women with extremely dense breasts (Saarenpää et al. 2001; Freer 2015). Mammography tends to underestimate tumor size and multifocality (i.e., simultaneous presence of tumor in multiple sites), and approximately 10% to 20% of palpable breast cancers are not visible at all, mainly as a result of insufficient contrast (Pisano 2000).

Ideally, the breast should be imaged in three dimensions with good contrast and high spatial resolution, while keeping the radiation dose to an acceptable level. Dedicated breast computed tomography (CT) was introduced almost 20 years ago, and has been tested with promising results (Boone et al. 2001; Lindfors et al. 2008; O’Connell et al. 2014). Important advances have been seen in recent years, as the digital breast tomosynthesis (DBT) technique has been developed and tested in screening trials (Ziedes des Plantes 1932; Gilbert et al. 2016). DBT is a 3D imaging technique where low-dose images are acquired and reconstructed into thin slices, reducing the effect of overlapping tissue, and facilitating breast cancer detection. It is expected that, in the next few years, DBT will be a strong alternative to planar mammography, both for screening and diagnosis (Kopans 2014). Studies have shown a significant increase in breast cancer detection (30%–40%), while the results on recall rates are slightly inconsistent (Lång et al. 2016). As a screening tool, reading time and radiation dose will be the main challenges, while in diagnosis the spatial resolution remains a principal assignment.

The X-ray methods are complemented by magnetic resonance imaging (MRI) and ultrasonic imaging (US). Although breast MRI is still largely experimental, it has been shown that it can be more sensitive than mammography or US (Lehman et al. 2007). Too many false positives remain a significant problem, as well as the cost and long acquisition time. Currently, MRI is used for screening women with an increased familial risk of breast cancer or for specific pre-operative purposes (Hakumäki 2016). A real benefit of MRI and US in comparison with X-ray imaging is the use of non-ionizing radiation.

### 51.1.4 From Absorption Contrast to Phase-Contrast

The emphasis in this Chapter is on X-ray phase-contrast mammography (PCM)—a quite recent X-ray imaging technology that has been developed to overcome the insufficient image contrast of the X-ray absorption contrast mammography (see Section IV, Chapters 49 and 50). A prime limitation to obtaining high contrast images in the clinic is the limitation on the dose delivered to the patient. This requires that the X-ray energy be high enough to limit absorbed dose, but that means lower contrast images. For soft tissue imaging at clinical energies or above, the image contrast due to phase-contrast is significantly higher than absorption contrast. Technical developments are being pursued extensively so that phase-contrast imaging could be adopted as an additional clinical tool for diagnosing clinically occult (i.e., not accompanied by detectable signs or symptoms) breast disorders. However, all these technologies are investigational, and their clinical applications, if any, will be determined by comprehensive scientific studies and regulatory approval.

X-ray PCM was reviewed recently (Keyriläinen et al. 2010). By that time, most experimental results were obtained by analyzer-based imaging (ABI) (see Section IV, Chapter 53), and several...
examples were illustrated in the review. The emphasis was in comparisons with clinical imaging, “reading” the mammographic signs by experienced radiologists, and in matching the images with the histopathology of the samples. Changes in the (supra) molecular structures were discussed in terms of small angle X-ray scattering (SAXS) from fibrous collagen, and clear correlations between the scattering signal and the cancer growth were demonstrated.

In the last few years there have been many new developments in X-ray PCM. Propagation-based imaging (PBI) has been used in pre-clinical studies (see Section IV, Chapter 50), and grating interferometry (GI) for differential phase-contrast (DPC) imaging. At the same time, there have been important advances in the use of conventional X-ray sources, and imaging using compact sources based on the method of inverse Compton scattering has been demonstrated. This chapter summarizes the present situation.

### 51.2 Theoretical Foundations and Practical Methods

#### 51.2.1 X-ray Phase and Amplitude

The basic theory of X-ray phase-contrast imaging is presented in Chapter 49. The results of that chapter are briefly summarized in this chapter, and practical applications to mammography are discussed. Special emphasis is given to visualization of signs of malignancy in phase-contrast images and their possible use in breast cancer diagnostics.

The response of an object to an incident X-ray beam is characterized by the refractive index, \( n = 1 - \delta + i\beta \). It is assumed that the variations of the optical density of the object are slow over length scales of the X-ray wavelength, \( \lambda \), which justifies the use of scalar paraxial fields in the description of wave propagation in a medium. The difference of \( n \) from unity is extremely small (of the order of \( 10^{-6} \) for hard X-rays). The real part \( \delta \) is related to the change of phase and the imaginary part \( \beta \) to the change of amplitude of the wave. The wave field on the optical axis at position \( z = z_0 \) downstream of the object, is given in Chapter 49, where \( \Phi(x,y,0) \) is the incident plane wave of unit intensity,

\[
\Phi(x,y,z_0) = \exp \left[ -ik\int_{0}^{z_0} (\delta(x,y,z) - i\beta(x,y,z))dz \right] \times \Phi(x,y,0)
\]  

(51.1)

The phase shift per unit path length is \( d\phi/dz = -k\delta(x,y,z) \), where \( k \) is the wave vector, and the corresponding amplitude shift is \( d\alpha/dz = -k\beta(x,y,z) \). The amplitude attenuation coefficient is \( \mu = 2k\beta = 4\pi\beta\lambda \). The amplitude reduction is due to scattering away from the forward direction, resonant (photoelectric), and non-resonant (elastic and inelastic). The phase shift of the resultant transmitted wave is due to the combination of forward elastic scattering with the incident wave (Suortti et al. 2013). Far from the absorption edges, \( \delta \) is proportional to the density of the object, \( \rho(x,y,z) \),

\[
\delta(x,y,z) = r_e^2N_A Z \rho(x,y,z) / 2\pi M
\]

(51.2)

where \( r_e \) is the classical electron radius, \( N_A \) Avogadro’s number, \( Z \) the atomic number, and \( M \) the atomic weight. Since \( M/Z \) is almost 2 for light elements,

\[
\delta = 1.35 \times 10^{-4} \lambda^2 [\text{nm}^2] / [\text{g/cm}^3]
\]

(51.3)

The numerical value of \( \delta \) is much larger than that of \( \beta \), in the case of breast tissue and 25 keV radiation \( \delta = 0.37 \times 10^{-4} \) and \( \beta = 0.208 \times 10^{-6} \). Over a given distance the relative phase change is three orders of magnitude larger than the relative amplitude change. Phase imaging is essentially that of mapping \( \delta(x,y,z) \) and, hence, the density of the object, and the contrast resolution is expected to be superior to the contrast resolution in attenuation imaging.

#### 51.2.2 Transport of Intensity and Phase Differential

At the exit of the object, \( z = z_o \), the beam is combined from the attenuated incident beam and the forward scattered beam. A detector at the exit records only the beam attenuation, but after a sufficient propagation distance the effects of phase change become visible in the beam intensity. Following the treatment in Chapter 49, the intensity at distance \( z - z_o \) (from the exit surface of the object to the detector plane) is given by

\[
I(x,y,z) = I(x,y,z_o) - [(z - z_o)/k][\text{grad}_x I(x,y,z_o) 
\times \text{grad}_y \delta(x,y,z_o) + I(x,y,z_o)\text{grad}_x^2 \delta(x,y,z_o)]
\]

(51.4)

The measurable intensity at position \( z \) downstream of the object contains three contributions. The first term, \( I(x,y,z_o) \), contains only attenuation in the object. The terms in the square brackets arise from the transverse (in the \( x,y \) plane) gradients \( \text{grad}_x \) and the transverse Laplacian \( \text{grad}_x^2 \), respectively. Variations of the gradients and Laplacian give rise to lateral variations of intensity, therefore to image contrast, which may be orders of magnitude larger than the absorption contrast.

The experimental methods of recording the lateral phase changes are discussed in subsequent sections, but some general comments are due. The refraction angle \( \alpha \) at an interface where the refractive index changes by \( \Delta \delta \) can be calculated from Snell’s law, \( \alpha = \Delta \delta \tan \theta \), where \( \theta \) is the angle between the incident beam and interface normal. The phase gradient in the direction \( y \) is \( d\phi/dy = k\alpha \). It is obvious that the interfaces that are (nearly) parallel to the beam give rise to strong refraction. The contrast at the edges of object structures is enhanced by the Laplacian term when the distance \( z - z_o \) is large. This is the main feature in propagation-based phase-contrast images.

The ultimate goal of phase-contrast imaging is 3D reconstruction of the refractive index decrement \( \delta(x,y,z) \), and, from that, the density variations of the object. Setting aside crystal interferometry, this means extracting the phase gradient from the refraction angle distribution or phase retrieval from the Laplacian. It is important that the angle \( \alpha \) at the exit is the sum of deviations along the beam path, so that CT reconstruction of the differential phase is possible from projections of the refraction angle using standard algorithms. On the other hand, in PBI the projected phase distribution must be retrieved from the
Laplacian term of the intensity distribution for CT reconstruction of phase $\phi$.

Scattering is considered a nuisance in absorption-based imaging, because it gives rise to a diffuse background. Phase reconstruction from the transmitted intensity distribution is the primary objective in phase-contrast imaging, but scattering away from the beam carries important information, which can be extracted by different imaging methods. The effects of scattering are observed as increased attenuation of the transmitted beam. The instrument may be tuned to record the scattering signal or even to record the scattered and transmitted beams simultaneously. The generic term for these modalities is dark field imaging (DFI).

51.2.3 Methods of Phase-contrast Imaging

Mammography (PCM)

Breast cancer causes changes in tissue structure on different length scales, ranging from large tumor masses to collagen strands, micro-calcifications, and the (supra) molecular level. The following section discusses different X-ray methods that are used to make these changes visible. The effects on intensity are summarized in Equation 51.4, which includes attenuation due to various forms of scattering, beam refraction, and redistribution of intensity at lateral edges of tissue density.

51.2.3.1 Crystal Interferometry

The advantage of crystal interferometry is direct detection of the phase of the wavefield. The method was introduced by Bonse and Hart (1965a), and applied in imaging by Momose (1995, 2003). The incident beam is divided into two coherent beams, the object is placed in one of the beams, and a phase shifter is placed in the reference beam. The beams are brought together, and the phase change due to the sample is determined from the interference pattern. The 3D distribution of $\delta$ (and the object density) is obtained by CT. The method works best for small and smooth phase gradients when unwrapping of $2\pi$ multiples of phase is not required.

Crystal interferometry has limited use in imaging because of the stringent requirements of stability of the perfect crystal device. However, as a direct method of phase mapping, crystal interferometry provides important reference to methods based on phase retrieval from differentials.

51.2.3.2 Propagation-Based Imaging (PBI)

PBI is the simplest method, because no X-ray optical devices are needed. The source must be small to provide transverse (spatial) coherence of the beam, but longitudinal (temporal) coherence is not critical, so that wide-band radiation from conventional sources can be used. Edge contrast due to redistribution of intensity is illustrated in Figure 51.1 (Zysk et al. 2012).

The phase changes are smooth and the Laplacian small except at the lateral edges, where the transverse phase profile changes abruptly. Sufficient distance between the object and the detector is required, typically a few meters. There are several methods for phase retrieval from the observed intensity distribution. These involve various approximations, which are needed to separate the contributions of absorption and phase. Various approaches are discussed in Chapter 49. Phase is the additive factor which is needed for CT reconstruction of the object morphology. There are recent analyses and comparisons of the methods (Burvall et al. 2011; Gureyev et al. 2014; Nesterets et al. 2015). Compared to methods where the phase gradient is usually observed in one direction only, PBI has the advantage of 2D recording of the Laplacian. Due to its experimental simplicity, PBI is probably the method that will have the widest clinical applications when the phase retrieval algorithms are routinely used.

51.2.3.3 Analyzer-Based Imaging (ABI)

ABI is the generic acronym for phase-contrast imaging methods based on the use of perfect crystal monochromators and analyzers (see Section IV, Chapter 53). Refraction contrast of X-rays was demonstrated in early experiments where conventional tube sources were used ( Förster et al. 1980; Podurets et al. 1989). There were also applications to soft tissue imaging (Ingal and Beliaevskaya 1995; Ingal et al. 1998), although the exposure times were long. Rapid developments of the ABI methods took place only when synchrotron radiation (SR) was introduced in this field (Chapman et al. 1997). The actual setting is that of the Bonse–Hart camera in its simplest form (Bonse and Hart 1965b, 1966). A parallel, monochromatic fan beam is obtained by Bragg

![FIGURE 51.1 Simulated images of a spherical micro-calcification in PBI with a Konica Minolta system. Blurring of intensity due to the source size is shown in the inserts. (Reprinted from Zysk, A.M. et al. 2012. Medical Physics 39:906–11. Copyright 2016, with kind permission from the American Association of Physicists in Medicine.)](image-url)
X-ray Phase-Contrast Mammography

**FIGURE 51.2** Standard ABI setup in the plane of diffraction (y,z). Conversion of the beam deviation to an intensity change is indicated at the working point L. (Reprinted from Keyriläinen, J. et al. 2008. *Radiology* 249:321–7. Copyright 2010, with kind permission from the Radiological Society of North America.)

Reflection from a perfect Si crystal. The beam traverses the object and is then reflected by the analyzer crystal. Usually the crystals are identical and set in the non-dispersive, antiparallel reflection geometry (Figure 51.2), and in the standard setup the tails of the rocking curve are not suppressed by multiple reflections.

The intrinsic analyzer rocking curve (RC) without the object is approximately triangular and the typical angular full width at half maximum (FWHM) is a few micro-radians (1 arcsec = 4.85 μrad). In transmission through the object a pencil beam is deviated by refraction, and attenuated by absorption and by scattering away from the forward direction. The transmitted beam is the refracted pencil beam “dressed” in a halo of scattering. The analyzer acts as an angular slit that passes the intensity distribution projected on the scattering plane (Suohonen et al. 2007). When the analyzer is rocked it is observed that the intrinsic RC is shifted by refraction and convolved by the projected scattering distribution.

ABI has been discussed recently in detail (Suortti et al. 2013). The overall goal is to describe the observed RC by a fitting function or by a few parameters that correspond to the phase variation and intensity of scattering. In practice, several working points (tilt angles of the analyzer) along the intrinsic RC are selected. Typical choices are indicated in Figure 51.2. At the deep slopes of the RC the refraction shift is converted to an intensity change. In the diffraction-enhanced imaging (DEI) algorithm the RC at the slopes is given by a first-order Taylor expansion, and the differential phase and the apparent absorption are solved (Chapman et al. 1997). Scattering increases apparent absorption, but it also broadens the RC. Higher order Taylor expansions and more working points are used to account for the effects of scattering. The difference between the observed and intrinsic RCs is analyzed in terms of central moments, which yields absorption, refraction, and scattering images. The results are reliable when the refraction angles and the width of the scattering distribution are small in comparison with the RC width. The algorithms are usually based on explicit or implicit use of Gaussian distributions, which are not sufficient to include the long tails of the observed RC, when scattering is strong. More general functions are used for adequate separation and mapping of absorption, refraction, and scattering distributions. The Voigt function is the convolution between a Gaussian and a Lorentzian. The Pearson VII function can be “tuned” from a Lorentzian to a modified Lorentzian, and to a Gaussian. These functions make possible accurate fitting to the observed RC, as discussed in Chapter 49.

### 51.2.3.4 Grating Interferometry (GI)

GI stands for grating interferometry. The method has its origins in visible light optics. The original observation of self-imaging of a diffraction grating dates back to early nineteenth century (Talbot 1836). In X-ray applications a phase grating is used. Parallel grooves of period p produce transverse variations of phase, typically a variation of π radians is used. Due to interference, a square-wave like intensity pattern of period p/2 is observed at fractional Talbot distances D,

$$D = mp^2/8\lambda,$$  \hspace{1cm} (51.5)

where m is an integer. An absorption grating of period p_2 = p/2 is placed in front of the detector, and the pattern is recorded by scanning the grating across the detector (phase stepping). The intensity varies approximately sinusoidally, as shown in Figure 51.3.

An object in front of or behind the phase grating modifies the intensity pattern by refraction, attenuation, and scattering. Evidently, transverse coherence over a phase grating period is required. The average intensity, a_0, the amplitude of intensity variation, a_1, and the phase shift, \phi_1, are recorded at each detector pixel. When compared with those without the object, three images are obtained: absorption, differential phase shift (refraction), and dark field (scattering). The main limitation to the use of the method in clinical imaging is the requirement of transverse coherence of the X-ray beam. The source must be small, and the distance to the interferometer sufficiently large. Both requirements reduce the available intensity. One solution is to use an extended source with an additional absorption grating,
which provides an array of small sources. This setup is called the Talbot-Lau interferometer (Pfeiffer et al. 2006). On the other hand, the requirement of longitudinal coherence is quite relaxed, so that broadband radiation from conventional or compact synchrotron sources can be used.

The phase gratings are usually manufactured on Si wafers by etching. The phase change in a groove of depth $h$ is $8kh$. For instance, for a phase shift of $\pi$ at 25 keV photon energy, $h = 32 \mu m$, and at 50 keV, $h = 64 \mu m$. The high aspect ratio required at high energies and good spatial resolution pose manufacturing challenges. Also, phase stepping of the absorption grating requires great precision and stability. As an alternative to mechanical stepping, electromagnetic phase stepping has been introduced (Miao et al. 2013). The gratings are held rigidly, but the source is moved by guiding the electron beam of the X-ray tube by a magnetic field. Another method that avoids the phase stepping has been developed (Koehler et al. 2015). In this slit-scanning method the object is moved laterally between the two gratings in a direction perpendicular to the grating lines. In practice, the object is held fixed and the two gratings, rigidly fixed to each other, are scanned. With continuous improvements, GI has become a versatile tool for phase-contrast imaging of objects of moderate size.

The phase and scanning gratings are periodic in one direction, so the images arise from beam deviation in that direction only. Separate perpendicular scans provide 2D images at the expense of doubling the radiation dose. Chess-board 2D gratings can be used (Kottler et al. 2007a; Zanette et al. 2011). Due to the technical complexity of 2D imaging, most interferometers are based on the use of 1D gratings.

### 51.2.3.5 Edge Illumination Imaging (EI)

EI stands for edge illumination imaging. There are several methods where the incident beam is periodically modulated by an absorption grating and the distortion of the regular pattern by the object is recorded. Talbot self-imaging of the grating is not used, since the distance of the pixel detector from the grating is chosen to provide sufficient angular resolution. The signals of absorption, refraction, and scattering are not as clearly separated as in GI, and the background is higher, but the methods are simple and easily implemented.

One of the variants of EI is the coded-aperture method, where the detector is divided by a mask into a pattern of sensitive and insensitive regions between adjacent pixels, and the same pattern is created in the beam incident on the object. The beams are deviated by refraction and scattering, which can be mapped by comparison with the reference image taken without the object. The coded-aperture setup and effects of refraction are shown in Figure 51.4. Applications to mammography have been discussed recently (Munro et al. 2013; Longo et al. 2015). There are promising perspectives for clinical imaging, because the setup is simple.

### 51.2.3.6 Phase-Contrast Imaging without Phase Retrieval

The above discussions are based on the assumption that the X-ray phase at the exit from the object is determined directly (crystal interferometry), from the differential phase (ABI, GI, EI), or from the Laplacian of the phase (PBI). Phase retrieval

---

**FIGURE 51.3** Schematic setup (a) of GI. The phase grating G1 is self-imaged at the fractional Talbot distance, $D$. The interference pattern is distorted by the sample, and the differential phase is recorded by scanning the absorption grating, G2, of half-period. The observed sinusoidal variation of intensity in a pixel is shown in (b). (a) Reprinted from *European Journal of Radiology*, 68S, Weitkamp, T. et al., X-ray phase radiography and tomography of soft tissue using grating interferometry, S13–S17, Copyright 2008, with permission from Elsevier; (b) Reprinted from *Scientific Reports*, 6, Gkoumas, S. et al., A generalized quantitative interpretation of dark field contrast for highly concentrated microsphere suspensions, 35259, Copyright 2016, with permission from Elsevier.)

**FIGURE 51.4** Diagram (a) of the EI principle and implementation (b) with divergent beams. (Reprinted with permission from Diemoz, P.C. et al., Sensitivity of laboratory based implementation of edge-illumination X-ray phase-contrast imaging. *Applied Physics Letters* 103:244104. Copyright 2013, American Institute of Physics.)
requires separation of the effects of absorption, refraction, and scattering, which are the primary signals from the experiment. In many cases these signals or their combination may be used without phase retrieval for adequate imaging of the object. These signals are discussed and compared in the following.

PBI emphasizes the lateral contours of the object, which may be sufficient for visualization of the object. The method works best for small objects where the structures are not superimposed. However, small structures in a uniform medium are highlighted. For the present context, it is important that thin collagen strands and micro-calcifications can be clearly seen in phase-contrast mammograms, because the uniform adipose tissue gives low contrast. Examples are shown in subsequent sections of this chapter.

ABI provides a clear distinction between the effects of absorption, refraction, and scattering. By appropriate choices of working points on the analyzer RC, these contributions can be mapped. In some experiments, the working point is at the top of the intrinsic RC. A combination of effects is recorded, which is useful for imaging, although different contributions are not separated. The intensity is reduced due to true absorption and by scattering away from the forward beam (sometimes called “extinction”). Refraction makes the working point slide off from the peak of the observed RC, but the direction is not recorded. The advantage of imaging at the top position (or close to it) is the maximum intensity and the enhancement of absorption by the refraction and scattering effects. In mammography, the top images have the closest resemblance to the clinical images, which facilitates the interpretation. On the other hand, angular deviation due to refraction results in an intensity change at the steep slopes of the analyzer RC, which may be converted to differential phase. Again, the external and internal contours are emphasized.

GI has certain similarities with standard ABI. When the intrinsic intensity curve in phase stepping is used as the reference, the differential phase due to the object is obtained from the shift of the intensity curve. However, when the phase step is 1/4 of the grating period, the working point is at the linear slope of the intensity curve, and the differential phase is obtained from the intensity change in the same way as from the slope image in ABI.

### 51.2.3.7 Dark field Imaging (DFI)

DFI is an acronym for dark field imaging, where the scattered beam is excluded from the final image. In the present context DFI rather means recording scattering separately. Scattering provides essential information about micrometer and sub-micrometer structures, that is, on the cellular and molecular level. There are several experimental possibilities. In standard ABI the working point may be chosen on the far tail of the RC, which corresponds to recording SAXS and USAXS, that is, ultra-SAXS by a Bonse–Hart camera. The use of a Laue-type (transmission) analyzer crystal allows the simultaneous recording of the diffracted and transmitted beams. The conceptual setup is shown in Figure 51.5.

![Figure 51.5 DFI with a Laue-type analyzer. Due to the Pendellösung effect, the non-scattered beam is directed to the 2θ angle, while the scattered and refracted beam is transmitted in the forward direction, providing a dark field image of the sample. (Reprinted with permission from Sunaguchi, N. et al., X-ray refraction-contrast computed tomography images using dark-field imaging optics. Applied Physics Letters 97:153701. Copyright 2010, American Institute of Physics.)](image-url)

The beam reflected by the first crystal is expanded and has very small divergence so that the Pendellösung effect is observed in the Laue crystal of appropriate thickness (James 1962). When the crystal is tuned to the peak (top) position the non-deviated beam is diffracted at angle 2θ, while the refracted and scattered parts pass through the crystal in the forward direction (Sunaguchi et al. 2010). Another possibility is to work on the far tail of the Laue crystal RC, where the scattered beam is diffracted, but the non-scattered beam is transmitted in the forward direction (Kitchen et al. 2011).

DFI is possible also in other imaging methods. The dark field (DF) signal in GI is recorded at a phase step (1/2)p, where the non-deviated beam is blocked. ABI has the advantage that the scattering signal is recorded separately, while in the other methods scattering may cause small modulation of the total recorded intensity. Use of the scattering signal has been limited in PCM, although it has been demonstrated to carry information of (supra) molecular changes related to cancer growth (Fernández et al. 2008). If DFI can be incorporated in the imaging methods it will greatly augment the diagnostic potential of PCM.

### 51.2.3.8 Projection, Computed Tomography, Tomosynthesis

The projection image given by Equation 51.4 has three terms: intensity reduced by resonant scattering (photoelectric effect) and by non-resonant scattering (elastic, nearly elastic, and Compton), losses due to beam deviation (refraction), and losses due to destructive interference. The last term is proportional to the Laplacian of the phase, and it becomes large and even dominant in the far field. The refraction loss also grows with distance, and that is exploited in EI. The near field intensity is analyzed in ABI and GI by narrow angular slits of a perfect crystal reflection or by an absorption grating, respectively.

In a projection image the images of successive layers of the object are superimposed. This is also the greatest weakness of standard projection mammography. The structures can be segmented to some degree by stereotactic imaging, but important details are often missed and their locations are uncertain. CT imaging of breasts will probably be the most important development in cancer diagnosis (O’Connell et al. 2014). Phase-contrast methods have a special role, because the much enhanced image contrast allows the use of clinically acceptable doses, which are insufficient for absorption-based imaging.
Along the X-ray beam path within the sample, the attenuation is described by \( \mu(x,y,z) \), refraction by the lateral phase gradient \( \nabla \phi(x,y,z) \), and scattering by coefficient \( \sigma(x,y,z) \). CT imaging is based on the assumption that, when the cumulative effects of these factors on a pencil beam are recorded and separated behind the sample, the values of \( \mu, \phi, \) and \( \sigma \) can be reconstructed from a sufficient number of projections. This implies that the pencil beam inside the object travels within the infinitesimal channel defined by the detector pixel. This is the concrete meaning of the “projection approximation” used in Section 51.2.1. In near field recording by ABI and GI this condition is fulfilled, but PBI deserves a closer look. The scalar components of the refraction angle in the plane of diffraction \((\gamma,\zeta)\) add up, and at the exit the angular deviation is the line integral of the refraction angles. When the \( y \)-direction is the rotation axis, the phase gradient \( \partial \phi(x,y,z)/\partial y \) is the same at all rotation angles, and the differential phase can be reconstructed with standard methods.

The scattering signal carries important information about object structures on a sub-micron level. Recording of the scattering signal is called DFI, which was discussed in a previous section. In GI and EI the total scattering signal has been used for object reconstruction and illustration of different tissue types (Zanette et al. 2012; Endrizzi et al. 2014). In ABI the one-dimensional projection of (U)SAXS can be recorded by varying the analyzer angle, like in a Bonse–Hart camera. The shape and size of the scattering particles are related to the scattering distribution through Fourier transform (Guinier 1963), but in practice the maximum information about the object structures contributing locally to (U)SAXS is probably a map of size distributions (Chen et al. 2010). For a detailed discussion on the use and information content of the scattering signal, the reader is referred to a review by the present authors (Suortti et al. 2013).

In PBI, the unprocessed intensity distribution reveals fine details of the internal and external contours of the object. However, these projection images are not used for CT reconstruction. The effects of absorption and wave propagation coexist, and, for a quantitative reconstruction of the object, that is, the local refractive index \( 1 - \delta(x,y,z) + i\beta(x,y,z) \), the phase \( \phi(x,y,z) \) and the absorption coefficient are retrieved using refined algorithms. These are usually based on the transport of intensity equation in the so-called homogeneous version, which may fail in imaging multi-material samples and large density variations. This is not the case in mammography, and it has been shown that, in comparison with the absorption-based CT, the image quality indicators increase by an order of magnitude (Gureyev et al. 2014; cf. Section 51.3.2).

In CT imaging the optimal number of projections, \( N_\text{o} \), depends on the diameter of the object, \( 2r \), and on the detector pixel size, \( w \), so that \( N_\text{o} = \pi r/w \). This becomes a very large number in high-resolution CT, and alternative methods for 3D imaging of the breast have been developed. The standard reconstruction using the filtered back projection algorithm may be replaced by other methods, such as the equally sloped tomography, to reduce the number of projections (Zhao et al. 2012). Tomosynthesis was introduced in the 1930s (Ziedes des Plantes 1932), and it has become a practical imaging modality due to fast high-resolution area detectors (Dobbins and Godfrey 2003). A limited number of projection radiographs at angular intervals of a few degrees are combined to bring a specific plane to sharp focus by the so-called shift-and-add reconstruction method. Tomosynthesis is particularly useful in mammography, where distinct features such as micro-calcifications and collagen strands can be highlighted (Wu et al. 2003; Park et al. 2007; Láng et al. 2014) (see Section II, Chapter 20, and Section IV, Chapter 52). Clinical tomosynthesis examinations utilize cone beam geometry and contact radiography, but extension to PCM by the PBI is possible, probably even with new, high-brightness X-ray tubes or other compact radiation sources. Tomosynthesis based on DFI by SR has been demonstrated (Shimao et al. 2008).

### 51.2.3.9 Comparison of PBI, ABI, and GI Methods

The actual phase-contrast images of the breast are affected by many factors, and fair comparisons may never be possible. From the clinical point of view, the most important aspect is the visibility of the signs of malignancy, and “reading” of the images is possible on different levels, from screening to detecting sub-micron changes in the tissue structures. To date, there are no comprehensive studies where the diagnostic capabilities and clinical value of the different methods of PCM have been compared. On the other hand, it is evident that all of the three methods make possible high-resolution 3D imaging of breasts with radiation doses far below the doses in conventional, absorption contrast methods. Each one of the methods has its advantages and weaknesses, and the choice is often based on availability or convenience.

Rather than ranking the phase-contrast methods, it is useful to study the signals and their use. Realistic phantoms can be built and corresponding images can be simulated to provide a common ground for analysis and comparisons. The effects of the actual experimental conditions can be brought in by measurements where the phantoms are imaged. Ideally, maps of the refractive index decrements \( \delta(x,y,z) \) and \( \beta(x,y,z) \) with error bars could be retrieved from the images. For quantitative comparisons, different indicators have been introduced, such as the signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), figure-of-merit (FoM), and a combined image quality index, \( Q_\delta \) (Diemoz et al. 2012a,b; Gureyev et al. 2014).

Images of a very simple phantom, a nylon wire, are shown in Figure 51.6 at different distances in PBI, and at different analyzer angles in ABI and at different phase steps in GI.

In PBI, a sufficient distance between the object and the detector is required to separate the intensity loss within the edge region and the increase of intensity outside the edge. In ABI, five different analyzer angles are chosen, at the top of the RC (100% intensity), at mid-slopes (50%), and in tails of the RC (10%). At the top position the beam slides off due to refraction, seen in the increasing intensity loss towards the edges. At the slope positions the beam slides up or down the RC, depending on the direction of the beam deviation and the sign of the derivative of the RC. The refraction contrast is at maximum at the edges of the object. At the tail positions large refraction makes the beam slide up the RC at one of the edges, giving strong contrast. The refraction contrast in GI is similar to that in ABI, as shown by images at increasing phase step values over one period, from 0 to 2.0 µm. The top position is between 0.75 and 1.0 µm, and the bottom position between 1.75 and 2.0 µm. The strongest refraction contrast is observed at the slope positions between 0.25 and 0.5 µm, and between 1.25 and 1.5 µm.
An FoM was calculated for the cases shown in Figure 51.6, and compared with the FoM derived from the experiment. The results depend on the width of the edge region considered. The intensity variation at the edges of an ideal phase object is shown in Figure 51.7. In PBI there is a sharp loss inside the edge and a narrow intensity peak outside. The intensity signal in the slope position in ABI or in GI is uni-modal, either positive or negative, and wider than in PBI. The observed signal is smeared by the point-spread-function of the instrument. In PBI, the detector resolution and the distance from the object must be sufficient to separate the positive and negative signals to avoid canceling the edge contrast. In the examples considered, FoM was calculated from the peak values of the intensity variation, rather than from the integral across the edge. The FoM at the slope position in ABI was about 3-times larger than the corresponding value in GI, and 10-times larger than the FoM of PBI at the maximum object-to-detector distance of 150 cm. The difference between ABI and GI is due to the steeper slope of the RC than that of the intensity variation in phase stepping in GI.

In the above example, no retrieval of the real and imaginary parts of the refractive index was performed. In a recent work, phantoms and breast tissue samples were studied under optimal conditions with PBI and ABI, including phase and absorption retrieval. The images were analyzed in terms of the image quality index, Qs, which combines the FoMs of the signal amplitudes and spatial resolution. PBI and ABI are comparable in image quality, and in both cases the contrast is an order of magnitude better than in absorption-based imaging (Gureyev et al. 2014).

Conventional mammography is performed at moderate X-ray photon energies, typically at about 20 keV (filtered radiation from a Mo, W, or Rh tube target). At higher energies, the differences in absorption between different tissue types decrease, leading to poor contrast. Phase-contrast prevails to high energies, but PBI, ABI, and GI are different in this respect. In PBI and GI the edge signal is proportional to $E^{-2}$, while in ABI the signal is proportional to $E^{-1}$. ABI-CT imaging of a breast tumor has been performed at 60 keV, which is probably an optimal energy with regard to image contrast versus absorbed radiation dose (Zhao et al. 2012).

### 51.3 Development and Present Status of Phase-Contrast Mammography (PCM)

All of the methods outlined in Section 51.1 have been employed in the study of phase-contrast imaging. Conventional sources, synchrotron sources, and new compact sources have been used as the...
source of the X-ray beams. There are two recent reviews of X-ray phase-contrast methods, with emphasis on mammography and possible clinical relevance (Bravin et al. 2013; Coan et al. 2013). In this section, PCM experiments using each technique are summarized with particular attention to the most recent developments.

51.3.1 Propagation-Based Imaging (PBI)

Propagation-based imaging, PBI, was one of the earliest imaging modalities at synchrotrons. The pioneering work by Wilkins et al. (1996) using a laboratory source and the implementation of PBI at synchrotron sources (Snigirev et al. 1995; Cloetens et al. 1996), motivated its development. In relating the history of the pre-clinical mammography project at the Elettra synchrotron in Trieste, Italy, Castelli et al. (2007) reported that the concept of human studies was initiated in 1991. At that time, there was no activity on PCM, although the work by Burattini et al. (1992, 1995) was on-going using monochromatic SR. The SYnchrotron Radiation for MEdical Physics (SYRMEP) beamline was constructed at Elettra (Castelli et al. 2007, 2011; Dreossi et al. 2008; Tromba et al. 2010) and optimized for the application of PBI and ABI. During the ensuing years, the decision to use PBI as the imaging modality on the SYRMEP beamline was made based on a number of experiments, some of which compared ABI and PBI (Arfelli et al. 1998, 2000). The project was implemented starting with phantom studies in 1996 and, following upgrades for the human studies, the pre-clinical in-vivo studies were carried out from 2006 to 2012.

The following is a brief description of the mammography imaging system (Tromba et al. 2010; Longo et al. 2014). The SYRMEP X-ray source is one of the bending magnets at Elettra. The patient is located at about 30 m from the source. At that location, the monochromatic beam has a useful area of 210 mm (horizontal) × 3.5 mm (vertical). The monochromator (double crystal silicon) is tunable in energy from 8.5 keV to 35 keV. For the mammography studies the energy was varied from 17 keV to 22 keV depending on the patient breast characteristics. The detector is positioned 2 m behind the patient. That is the optimal distance for the development of the edge-enhancement phase-contrast.

Due to the fixed, laminar geometry of the synchrotron beam, it is necessary to translate the patient vertically to produce a planar projection image. Using a screen-film detector, the detector and the patient must be vertically translated synchronously. The SYRMEP patient support has the patient lying in a prone position with the breast hanging below the support. For planar imaging the breast is compressed during translation. For CT imaging, the breast is constrained and rotation of the patient occurs with the breast at the center of rotation.

In the clinical study, the selection of X-ray energy for each procedure was evaluated for the different breast thickness and glandularity classes using a set of standard slabs simulating breast tissue. These were exposed at the Trieste Hospital using a clinical mammography unit and at the beamline to evaluate the corresponding mean glandular dose (MGD). MGD is the radiation dose quantity that is considered to represent the carcinogenic
risk from an X-ray mammography examination. The sizes and compositions of mammary glands vary widely, and thus a standard dosimetry procedure is to evaluate the MGD for a 45-mm-thick compressed breast of average composition. Mammography accreditation programs prescribe the MGD limits to 2 to 3 mGy for a compressed breast. For each breast thickness and density class, the lowest X-ray energy was chosen such that the MGD with SR PBI was less than or equal to the dose delivered during clinical mammography.

Eighty-two patients were selected between March 2006 and May 2012, on the basis of the enrollment criteria approved by the local ethics committee. The first study, which included 71 patients, was based on a mammographic screen-film system (Castelli et al. 2011). Moreover, a group of 11 patients was studied using a computed radiology system (Quai et al. 2013). Detailed reports on the stages of the human imaging project have been given (Castelli et al. 2007, 2011; Dreossi et al. 2008), with a final summary report by Longo (2016). Figure 51.8 is an example of the comparison between a standard clinical digital mammogram and one obtained with PBI (Dreossi et al. 2008).

A mass is shown enlarged in the insets. In the digital mammogram, the margins appear partly circumscribed and partly indistinct, leading to an uncertain diagnosis. Conversely, in the PBI image, the margins are micro-lobulated and partly spiculated, indicating a probable breast cancer, as was later confirmed by histology.

To evaluate PBI mammography, both image quality and diagnostic results were evaluated (Longo et al. 2014). It should be noted that, in the publications, the authors refer to PBI as PPCI (propagation-based phase-contrast imaging). The image quality analysis was based on the comparative evaluation of the visibility of the breast abnormalities and of the glandular structure. The diagnoses based on the digital mammography (DM) and on the PBI exams were compared with the Gold Standard (biopsy or 1-year follow-up), and both PBI mammography and DM specificities were calculated. A statistically significant increment was observed using PBI, thus suggesting that PBI mammography can be used to clarify cases of questionable or suspicious breast abnormalities identified by DM. Figure 51.9 shows the summary histograms of the scores of the relative visibility of (a) breast abnormalities and (b) glandular structure (Longo et al. 2014). In this analysis, a score of 1 meant excellent visibility in DM and poor in PPCI; a score of 2 or 3 showed that visibility was progressively lower in DM, but better than
that in PPCI; a score of 4 showed equal visibility with the two techniques; a score of 5 or 6 meant visibility was progressively better in PPCI than in DM; and a score of 7 implied excellent visibility in PPCI and poor visibility in DM. In their discussion, Longo et al. (2014) stated clearly the superiority of the PPCI images over those with DM.

The second phase of the SYRMEP human mammography pre-clinical studies is the development of CT imaging using the PBI imaging system. The project is called SYNchrotron Radiation for MAmmography (SYRMA)-CT, with the aim of setting-up the first clinical trial of phase-contrast breast CT with SR. The use of CT imaging or tomosynthesis is becoming common in clinical mammography to produce 3D images. The 3D imaging overcomes some of the severe diagnostic limitations of the standard projection imaging. Preliminary studies for CT imaging at SYRMEP started with work by Pani et al. (2004). With the completion of the planar mammography imaging program, attention is now being given to implementation of CT imaging for the future human studies (Longo 2016). Reconstruction of PBI images in CT mode requires that phase retrieval be applied to the data prior to the image reconstruction, in order to optimize the contrast in the images. A number of algorithms have been developed and tested in order to optimize the design of the CT mammography system at SYRMEP (Gureyev et al. 2014; Longo et al. 2014; Nesterets et al. 2015; Pacile et al. 2015).

Longo et al. (2016) reported the first phantom and breast tissue images taken with the CT system in the SYRMA-CT project. In order to combine high image quality and low delivered dose a number of innovative elements have been incorporated into the system: a CdTe single photon-counting detector, state-of-the-art CT reconstruction and phase retrieval algorithms, and the use of limited numbers of projections for dose reduction. A Monte Carlo model has been developed for dose calculation. In this study, high isotropic spatial resolution ($120 \, \mu m)^3$ CT scans of phantoms and excised breast tissue with dimensions and attenuation similar to a human breast were acquired, delivering MGDs of $0.6 \, mGy$ with a reduced number of projections, the spatial resolution was found to be equal to filtered back projection utilizing a 4-fold higher dose, while the CNR was reduced by 30%. These first results indicate the feasibility of clinical breast CT with the SYRMA-CT system.

Ultimately the goal is to introduce PBI into clinical mammography. The significant enhancement of the diagnostic quality of the images has been proven by the SYRMEP projects. Tanaka et al. (2005) reported trials using a digital full-field mammography system created by Konica Minolta using phase-contrast. The system consists of a mammography unit, a computed radiology unit, and a photo-thermographic printer. Full-field digital PCM images of phantoms and in-vivo breasts were compared with conventional screen-film mammography. The phantom images and clinical images of 38 patients were evaluated for diagnosis of mass and micro-calcifications. In both measures, the PCM clinical images were superior to those of the screen-film mammograms.

### 51.3.2 Analyzer-Based Imaging (ABI)

ABI was the first application in the field of PCM. Following the pioneering work of Förster et al. (1980), Davis et al. (1995) Ingal and Beliaevskaya (1995) and Ingal et al. (1998) used a basic two crystal ABI setup on a conventional laboratory X-ray source to analyze excised breast tissue containing various malignant and benign tumors, as well as calcifications. They showed the enhancement of mammographic radiology features compared to conventional absorption images as they varied the position of the analyzer crystal on the RC. Although they did not quantify the enhancement due to phase-contrast mechanisms, they clearly showed that phase-contrast imaging could be useful in the visualization of breast anomalies. In particular, the refraction contrast combined with the absorption signal proved to be useful. Perhaps most importantly, these experiments demonstrated that the coherence of the source was not critical to obtaining phase information. The low flux available from their X-ray generator and the film systems used for data collections had the effect of very long imaging times and high radiation doses. With the phase information and the use of the film detectors with clinical spatial resolution, the images did show the changes in parenchyma structure. Parenchyma consists of the functional elements of an organ, as distinguished from supporting or connective tissue. These changes were due to malignancy and micro-calcifications down to 50 microns in size, with the results verified by histological examination. Overall, the ABI images were superior to the standard absorption images to which they were compared. With improvements in the X-ray source and detector efficiency, they concluded that a mammography system with exposures of less than 1 second would be feasible.

The use of SR as a probe for mammography had its origins in the work of Burattini et al. (1992, 1995). They explored the image contrast enhancement in absorption images of human breast tissue due to the use of the highly monochromatic SR. They did not explore phase-contrast effects in their work, but the improved image quality motivated Johnston et al. (1996) to quantitatively study the imaging of mammography phantoms at the National Synchrotron Light Source (NSLS) in Upton, NY. In the course of that work, a crystal analyzer was introduced both as an anti-scatter optic and a means of studying the scattered radiation (Chapman et al. 1996, 1997, 1998). This was the first ABI setup at a synchrotron. The authors used the term diffraction-enhanced imaging (DEI) to refer to the ABI setup, coupled with their image analysis methods. In addition, a computed radiology system consisting of image plates and reader was implemented, thus making the imaging system comparable to those being introduced into the clinic.

The impact of these experiments on PCM was extremely important. From the earliest images obtained with mammography phantoms and the analyzer crystal, the concept of DEI was developed. With a first-order approximation to the slope of the RC, the use of two images on opposite sides of the analyzer RC to create separate “apparent absorption” and refraction images was
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a major breakthrough in image analyses. The apparent absorption image contains the true absorption, as well as additional contrast due to the rejection of SAXS by the analyzer. It was shown that the scatter can be detected by working at positions of the analyzer far out on the RC. Thus, various images could be produced for comparison with standard absorption radiographs (obtained with clinical sources or synchrotron beams). Images at the different positions have unique properties that enhance the visualization of breast tissues and the diagnostic quality.

For example, with the analyzer set at the 1/2 FWHM position, which has the maximum slope, the image is dominated by the refraction effects. Those images appear very different from those generally used in clinical diagnostics, and are difficult for radiologists to interpret. If the analyzer is set to the peak reflectivity point, the “top” position, then the image contains the absorption, the extinction due to scatter rejection, and some refraction information. Those images appear similar to but clearer than clinical images. The scatter signal was not used explicitly to form an image in these experiments, although it can contribute strongly to the visualization of calcifications and fibrous structures due to the length scales associated with such objects.

The radiation dose delivered in these experiments was often higher than clinical doses. That is not an intrinsic property of the technique, rather it was just that for proof-of-principle experiments it was necessary to obtain the most information. The authors did take images at spatial resolutions comparable to clinical imaging. One key variable with ABI that can lead to reduced dose to the sample is the ability to tune the energy to optimize contrast. ABI can be used at clinical energies (typically 23–33 kV) in the 17 to 22 keV range, or it can be used at much higher energies where the dose due to absorption is low (and consequently the absorption image is weak), but where the refraction remains dominant.

Pisano et al. (2000) presented a detailed summary discussion of the results obtained at the NSLS. Among many findings they state that the increased visibility of infiltrating lobular carcinoma, a frequently occult lesion, indicates that ABI could become an important clinical tool. They made comments and recommendations on the requirements necessary for ABI to become a clinical tool. Figure 51.10 illustrates the increased visibility of invasive lobular carcinoma in phase-contrast (DEI refraction) images, compared to absorption images taken without an analyzer. The DEI image showed improved visibility of fine lines (arrows in Figure 51.10a,b). Figure 51.10c reveals the invasive lobular carcinoma (arrows).

Some of the issues raised were the need for the development of clinical based X-ray sources to provide the high flux and high energy necessary for the monochromatic beam exposures on clinical time scales of seconds, the development of a robust ABI system capable of working in a clinical environment, advanced digital detectors, and image processing that can result in images that can be read by radiologists with proper training.

One very interesting study by Arfelli et al. (2000) was done at the SYRMEP beamline at the Elettra synchrotron. As part of the development of human mammography pre-clinical trials, the SYRMA project, a direct comparison of the diagnostic quality of breast tissue images obtained with the ABI technique and with PBI, was carried out. Overall, the results obtained by ABI and PBI were comparable, and both were always superior to standard absorption-based projection imaging. Compared with conventional mammography, phase-contrast and diffraction imaging result in strong enhancement of image contrast and increased visibility of small details. Because of the improved image contrast and detail visibility, these phase-detection techniques may be applied effectively in the field of mammography.

FIGURE 51.10 Comparison of (a) digital synchrotron radiograph and (b) DEI image of a specimen with invasive lobular carcinoma at NSLS. The photomicrograph (c) shows the carcinoma corresponding to the DEI images. (Reprinted from Pisano, E. et al. 2000. Radiology 214:895–901. Copyright 2013, with kind permission from the Radiological Society of North America.)
for both solving ambiguous cases and allowing earlier diagnosis of malignant lesions.

In parallel with the development of stable ABI imaging systems at synchrotrons and on laboratory sources, there were efforts to develop algorithms that would more accurately extract the absorption, refraction, and scattering information from the data. It was recognized very early that the first-order linear approximation to the RC was inadequate, especially for the scattering image. Pagot et al. (2003) and Wernick et al. (2003) showed that, by taking multiple images at a minimum of three positions on the RC, the information could better represent the underlying structures and scatter. Many forms of approximations to, and calculations of, the RC have been developed in Chapter 49.

Efforts in the development of planar PCM were continued at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France. Of particular interest is the work of Keyriläinen et al. (2005), in which detailed comparisons of the phase-contrast ABI projection images and the sample histopathology were carried out. Six excised human breast tissue specimens carrying benign and malignant tumors were examined with the DEI technique. DEI images were compared with diagnostic screen-film mammograms, and the correlation with histological information of the specimens was established. The enhanced visibility of calcifications, some of which were smaller than 0.15 mm in diameter, was reported. Fine details of the structures such as strands of collagen and contours between glandular and adipose tissue, which were barely visible at the contrast detection limit in the conventional absorption-based mammograms, were clearly visible in the diffraction-enhanced images. Microscopic study of the stained histopathology sections unequivocally confirmed the correlation of the radiographic findings with the morphologic changes in specimens. An increased soft tissue contrast and a combination of information obtained with DEI images provided better visibility of mammographically indistinguishable features. This kind of additional structural information of the breast tissue is required to improve assessment accuracy and earlier detection of the breast lesions.

The need to develop a clinical source capable of ABI PCM was pursued and reported by Parham et al. (2009). They described the design, construction, and performance of a DEI system using a commercially available tungsten anode X-ray tube, and reported the first high-quality low-dose diffraction-enhanced images of full-thickness human tissue specimens. Images acquired using this system successfully demonstrated all three DEI contrast mechanisms. Flux measurements acquired using this 1 kW prototype system demonstrated that this design could be scaled to use a more powerful 60-kW X-ray tube to generate similar images with an image time of approximately 30 seconds. This single-crystal pair design could be further modified to allow for an array of crystals to reduce clinical image times to less than 3 seconds. The advent of more powerful compact sources (Bravin et al. 2013) and the more robust technologies such as grating interferometers may ultimately supersede the implementation of ABI on such clinical sources.

As with clinical mammography, the efforts at synchrotrons to develop high contrast, low-dose phase-contrast CT were started at the ESRF. It had been shown (Dilmanian et al. 2000) that the phase information from ABI imaging was preserved in the reconstruction of CT images. Several experiments on the CT imaging of excised breast tissue with comparisons to standard clinical CT imaging, MRI, and pathologies have been reported (Fiedler et al. 2004; Bravin et al. 2007; Keyriläinen et al. 2008, 2010, 2011). The important efforts in these experiments was to obtain CT images with high-resolution using digital detectors, doses equivalent or less than clinical CT by use of energies in the range of 30 keV, and image reconstruction useful to clinical radiologists.

One of the limitations in all of the preceding experiments was that the samples were excised human breast tissues of varying limited sizes (less than 9 cm). They were not full breasts, which would require significantly higher monochromatic energies. Sztrőkay et al. (2012) reported imaging of a whole breast at doses higher than clinical values. Following the recommendations from that experiment, and using advanced algorithms for phase retrieval and reconstruction, Zhao et al. (2012) reported a high-resolution, low-dose phase-contrast X-ray tomographic method for 3D diagnosis of human breast cancers. Using the ESRF synchrotron, they imaged a human breast in 3D and identified a malignant cancer. The pixel size was 92 microns, and the radiation dose was less than that of dual-view mammography. According to a blind evaluation by five independent radiologists, the method could reduce the radiation dose and acquisition time by ~74% relative to conventional phase-contrast X-ray tomography, while maintaining high image resolution and image contrast.

The most recent efforts to advance ABI as a research or clinical modality have centered on optimization of the many parameters available. One study by Brun et al. (2014) developed a segmentation algorithm that is task-based, allowing the boundaries of tumors in ABI images to be defined with minimal human intervention. Gureyev et al. (2014) reported the results of a systematic study of phase-contrast X-ray CT in the propagation-based and analyzer-based modes using specially designed phantoms and excised breast tissue samples. The study was aimed at the quantitative evaluation and subsequent optimization with respect to detection of small tumors in breast tissue. They determined the effects of phase-contrast and phase retrieval on key imaging parameters such as spatial resolution, CNR, X-ray dose, and a recently proposed “intrinsic quality” characteristic Q5, which combines the image noise with the spatial resolution. They demonstrated that some of the methods evaluated lead to substantial (more than 20-fold) improvement in the CNR and intrinsic quality of the reconstructed tomographic images compared with conventional techniques, with the measured characteristics being in good agreement with the corresponding theoretical estimates. This improvement also corresponded to an approximately 400-fold reduction in the X-ray dose, compared with conventional absorption-based imaging of excised breast tissue.

The use of tomosynthesis with advanced reconstruction algorithms instead of full CT imaging was an important factor in the dose reduction for both ABI-CT and PBI-CT.

DFI, as presented in Section 51.2.3.7, has also been employed using the ABI technology. This technology has been pursued for many years by Ando et al. (2004, 2014) as a very highly sensitive means of measuring the scattering image of an object. In developing applications to biomedicine, they have reported some imaging of excised breast tissue.
51.3.3 Grating Interferometry (GI)

The development of GI as an imaging modality at both synchrotron sources and on laboratory sources started with the work of Weitkamp et al. (2005, 2008) and Pfeiffer et al. (2006, 2008). Since then there have been many experiments and developments in applying the techniques to mammography. In order to clearly present the current status of GI mammography, the developments are divided into three main themes: (1) Tissue Characterization, (2) Computed Tomography and Tomosynthesis, and (3) Implementation of GI on Laboratory, Clinical, and Compact Sources. The projects have been carried out on laboratory X-ray sources and at synchrotrons when the “Gold Standard” source was required. In all cases, the aim was to produce clinically relevant images at low radiation dose, high spatial resolution, and readable by radiologists in the clinic.

51.3.3.1 GI Mammography: Tissue Characterization

Stampanoni et al. (2011, 2013) published the first experimental evaluation of native breast tissue using GI. In many ways this was a landmark program in PCM. Using a laboratory X-ray source and a Talbot-Lau grating interferometer they imaged whole native breast tissue with a thickness of 4.5 cm. This proof-of-principle experiment clearly showed improved tumor visualization and discrimination between scars, breast tissue, and invasive tumors in the DPC and DF projection images. The images were systematically compared to findings with state-of-the-art radiological mammography imaging systems. One of the key features of this work was the introduction of the concept of mammoDPC, or DPC in mammography. Cognizant of the problems that radiologists have in interpreting the refraction images and DF images that are produced through image processing of the GI images, they developed reconstruction algorithms that fused the absorption and refraction (DPC) images, and then applied the DF scattering information. The significant increase in diagnostic information in the mammoDPC images is shown in Figure 51.11.

These images were interpretable by skilled radiologists. The publications contain many significant references to the image processing procedures. One main point made in this work was that the successful transition of this technology to clinical use is strongly related to image post-processing.

Therefore, advanced algorithms must be developed to exploit the added value of the mammoDPC technique, including image de-noising, image fusion, and features extractions. The DPC images are particularly sensitive to high spatial frequencies such as edges of structures, whereas small calcifications are highlighted in the DF. Although the radiation dose was about 26 mSv, an order of magnitude higher than conventional mammography, improvements in the system were clearly defined that could reduce the dose to clinical levels.

These experiments primarily reconstructed images providing the absorption and differential phase images, supplemented by the DF scattering information. In the samples they used there were not a large number of calcifications, and DF images were not highlighted. Anton et al. (2013) specifically studied grating-based projection DFI of human breast tissue. Their work emphasized the much higher tumor contrast in DFI due to the visualization of calcifications. They presented the results of a comparative study of breast tissue, including pre-surgical tomosynthesis, surgical resection, conventional mammographic imaging, DF studies, and finally histopathology. A full treatment and analysis of contrast due to absorption and DFI showed a much higher contrast of calcifications with DFI. The size of the calcifications ranged from 3 to 30 microns, much smaller than the detector pitch. The end result was that DFI may provide a means of diagnostic interpretation of calcifications.

A follow-up study on DF signals due to micrometer-sized calcifications was carried out by Michel et al. (2013). These studies, on whole breast and resected tissues, confirmed the enhanced visibility of calcifications and high spatial frequency structures using the DF projection images, in correlation with the phase-contrast and absorption images. Micro-calcifications do not show on absorption images, but are highly visible in DF images.

FIGURE 51.11 Image fusion result of a region of interest of an excised breast sample. The phase-enhanced image (b) contains the information from the absorption and enhanced detailed features from both differential phase and scattering images. It shows an improved sharpness compared to the absorption image (a). Some detailed features, which are hardly seen and do not manifest in the absorption image, are indicated by white arrows. (The source of the material Stampanoni, M. et al., Journal of Instrumentation, 2013, Institute of Physics is acknowledged.)
Simulations for the DFI were in agreement with the experimental results.

Wang et al. (2014) showed that it is possible to differentiate the two types of calcifications by measuring the ratio of scattering (DF image) and the absorption image. This may lead to \textit{in-vivo} classification for biopsy guidance or diagnosis.

Most GI imaging has been done with a single orientation of the gratings relative to the sample. This means that the images are showing phase-contrast information primarily in the direction perpendicular to the grating lines. Scherer et al. (2014) showed clearly that the inherently anisotropic imaging sensitivity of the mono-directional approach yields insufficient diagnostic information, and has low diagnostic sensitivity to highly oriented structures. They reported an experiment designed to study the importance of bi-directional scanning. Using a rotating anode source, a GI system in a projection imaging mode, and a full dissected breast, they applied their fusion algorithms to images taken with single and bi-directional scanning. The bi-directional scans showed high detectability of early tumors, high frequency features in all directions, and the potential for characterization of tumors. Although the radiation doses were very high, the importance of bi-directional scanning was clearly demonstrated by the enhanced tumor branch visibility (see Figure 51.12). The concept of 2D gratings was presented with reference to Zanette et al. (2011).

Hauser et al. (2014) carried out a statistical evaluation of the imaging capabilities of mammoDPC compared to digital absorption mammography. They designed two reader studies which involved mastectomy specimens of 33 patients and six breast radiologists. Mammograms of the freshly resected breasts were obtained with absorption-based clinical DM. Furthermore, absorption-based DM and phase-contrast-enhanced mammography (mammoDPC) were acquired simultaneously on an experimental projection imaging setup, as described in the study of Stampanoni et al. (2011).

The results of the comparison revealed the general quality of the images to be significantly superior in sharpness, lesion delineation, and the general visibility of calcifications, and delineation of anatomic components of the specimens (surface structures) was significantly sharper. Spiculations were significantly better identified, and the overall clinically relevant information provided by mammoDPC was judged to be superior. However, it must be noted that this proof of principle study had to be conducted with high-statistic measurements and, thus, the dose delivered was very high compared to clinical levels, and the time of acquisition was very long.

In a similar study, Grandl et al. (2015) used a laboratory source of X-rays with a Talbot-Lau grating interferometer system to evaluate improvement of visualization of breast cancer features in multifocal carcinoma. In projection imaging mode they obtained absorption, phase-contrast, and DF mammography images of dissected breast tissue, and compared them with pre-operative \textit{in-vivo} imaging, post-operative histopathological analysis, and \textit{ex-vivo} digital mammograms. An example of such

\begin{figure}[ht]
\centering
\includegraphics[width=\textwidth]{figure51-12.png}
\caption{Two-directional, grating-based mammograms of an invasive ductal carcinoma. Two-directional differential phase \( \delta \phi_x \) (a), \( \delta \phi_y \) (b), and sharpened, two-dimensional integrated phase image \( \Phi_s \) (c). Dark field Dx (d), Dy (e), and mean dark field D image (f). Arrows indicate the direction of scanning. The boxes indicate tumor branches exclusively perceivable in the images obtained with scanning performed in the x- or y-direction, respectively. (Reprinted from Scherer K. et al. 2014. \textit{PLoS One} 9:e93502. Copyright 2014, with kind permission from the Public Library of Science.)}
\end{figure}
a comparison and analysis is shown in Figure 51.13, along with the detailed description of the imaging parameters. Their key result was that, in the diagnosis of multifocal tumor growth, DF mammography is superior to standard DM. The resolution of small, calcified tumor nodules, demarcation of boundaries, and spiculated soft tissue strands was better.

51.3.3.2 GI Mammography: Computed Tomography and Tomosynthesis

The use of CT imaging for mammography is now becoming a clinical modality (O’Connell et al. 2014). The CT images overcome the common problems in current DM of the projection of overlying structures and occlusion of tumors and associated micro-calcifications. In the studies of the potential of phase-contrast CT (PC-CT) using GI, experiments have been carried out at brilliant synchrotron sources (Sztrokay et al. 2012, 2013; Schleede et al. 2014) and on conventional laboratory sources (Grandl et al. 2013, 2014). These experiments focused on comparisons of visualization and diagnostic information available from PC-CT compared to standard absorption DM. Therefore, the experiments were at significantly higher radiation dose levels than clinical values. The use of tomosynthesis instead of full CT is one means of significantly lowering the dose levels, but at the cost of reduced information on the structures. Advanced image processing algorithms for image reconstruction and phase retrieval are being developed and applied to the PC-CT images.

Based on the successful demonstration of X-ray PC-CT applied to soft tissue imaging (Donath et al. 2010), Sztrokay et al. (2013) assessed the use of GI based X-ray PC-CT for ductal carcinoma in-situ and an invasive ductal carcinoma. They employed a GI system at the ESRF using monochromatic radiation at 23 keV at high spatial resolution of about 30 microns. The dose to the samples was significantly above clinically acceptable levels. The phase-contrast and absorption images were compared with histopathology. The PC-CT images had a CNR of 9.6 compared to that of the absorption-based images of 0.27. The main conclusion was that PC-CT may allow the differentiation between invasive carcinoma and intra-ductal carcinoma and healthy breast tissue.
Clinical applications of PC-CT will depend on translation of the GI Talbot-Lau phase-contrast imaging technique to clinical sources, either based on standard X-ray technology or new compact sources. Grandl et al. (2013) demonstrated the potential of PC-CT on a conventional laboratory source in a study evaluating PC-CT for imaging breast tissue. Phase-contrast and absorption 3D datasets of the ex-vivo breast specimens were recorded and reconstructed. The images were matched with histological sections. The visualization of selected histological findings in phase-contrast was compared to the absorption contrast. The authors showed that PC-CT using a polychromatic X-ray source provides complementary information to absorption contrast. They did note, however, that the spatial resolution of the PC-CT images was inferior to that of images taken at a synchrotron, but was not detrimental to image visualization.

With the growing use of tomosynthesis mammography in the clinic, the concept of phase-contrast tomosynthesis is a natural advancement. Schleede et al. (2014) used monochromatic X-rays from a beamline at the ESRF to apply recently developed phase-contrast methods to obtain PC-CT and absorption-based CT images of breast tissue. Datasets were taken in the tomosynthesis mode with 61 projections and then reconstructed to yield the 3D image. The voxel size for this work was 30 microns, comparable to or better than that of clinical tomosynthesis. Figure 51.14 shows how tomosynthesis enhances the visibility of the breast morphology, in particular a parenchymal necrosis not visible in projection images. One limitation of this study was that it concentrated on the use of the DPC images rather than the DF images that are superior in detection of micro-calcifications (Stampanoni et al. 2011; Anton et al. 2013).

Grandl et al. (2014) have used a Talbot-Lau grating interferometer on a laboratory source to study the visualization and characterization of breast fibroadenomas. The samples were excised breast tissues containing fibroadenomas and other benign changes. This experiment also focused on the use of the DPC image, and not the DF image. The analysis necessary to develop DF-CT images is still under development. The authors concluded that the grating-based PC-CT showed improved differentiation of fine structures and accurate depiction of strands of fibrous tissue within the fibroadenomas, as well as other diagnostically important outcomes. This work was done at very high dose levels compared to acceptable clinical levels.

### 51.3.3.3 GI Mammography: Laboratory, Clinical, and Compact Sources

Many of the GI experiments described have been carried out on conventional laboratory sources. They have been proof-of-principle studies to determine the feasibility of GI-PC imaging, both in radiography and CT. The visibility and diagnostic quality of the breast tissue images have been optimized by using high radiation doses. The use of conventional sources has been demonstrated to produce excellent multi-modality images (absorption, differential phase-contrast, dark field). The authors have frequently outlined improvements to the experimental setups that would reduce the dose and exposure times; for example, high efficiency digital detectors, tomosynthesis, development of compact sources with higher flux, and working with optimally designed Talbot-Lau systems. There are now several examples of PCM using conventional and newly developed compact sources.
which show the feasibility of low-dose, fast exposure, high SNR mammography.

Gromann et al. (2016) optimized the parameters of a Talbot-Lau interferometer on a rotating anode laboratory source. By working at a high Talbot order, the signal-to-noise level in the images was sufficient to allow high visibility phantom and excised breast tissue images at a dose level of only 3 mGy (see Figure 51.15).

The breast tissue was a freshly dissected breast compressed to 4 cm. Images from the optimized system were compared with the same samples imaged on a previously used non-optimized interferometer, which delivered a dose of 60 mGy (Scherer et al. 2014). Gromann et al. (2016) discussed the measures required to produce a clinically compatible grating-based DPC mammography system. The key change would be to optimize the grating periods to preserve the high Talbot order, but constrain the dimensions of the system to be clinically compatible.

One of the limitations of incorporating grating-based DPC into clinical imaging is the requirement of stepping one grating relative to another, in order to produce the phase-contrast dataset that is then analyzed to produce the absorption, DPC, and DF images. Kottler et al. (2007b) developed a slit-scanning technique for phase retrieval that does not require stepping of the gratings. The phase retrieval is obtained by moving the object on a path perpendicular to the grating direction and the optical axis. The relative position of the gratings does not change. Koehler et al. (2015) adapted the slit-scanning technique to a clinically compatible source. Instead of moving the sample they created the same effect by moving the gratings and detector with the sample held fixed. The Talbot-Lau grating system was installed on a modified clinical multi-slit scanning mammography unit. Dose delivered to the phantoms was of the order of 1.9 mGy, and scan times were compliant with current mammography standards. Reconstructed images of absorption, phase-contrast, and small angle scattering (DF image) of phantoms and of a fish were presented. With a number of modifications that were discussed, the system could be adapted for in-vivo DPC mammography.

The first application of GI PCM using a compact synchrotron light source was reported by Schleede et al. (2012). They installed a grating-based interferometer on the Compact Light Source (CLS) manufactured by Lyncean Technologies. The CLS is an inverse Compton-based SR source that provides X-rays with high flux, narrow bandwidth, and spatial coherence. The X-ray energy used in these experiments was 21 keV. The set-up was used for high sensitivity absorption, DPC, and DF imaging. Applications of this technique to mammography require much more study of CNRs, acceptable radiation doses of 0.7 to 3.0 mGy. Applications of this technique to mammography require much more study of CNRs, SNRs, evaluation of significant numbers of breast tissue samples, and development of image processing algorithms.

51.3.4 Edge Illumination Imaging (EI)

Following the original work by Olivo and Speller (2007) on coded apertures for phase-contrast imaging, the first report of the application of the edge illumination imaging (EI) to mammography was by Olivo et al. (2013) and Diemoz et al. (2013). They termed the method XPCI for X-ray phase-contrast imaging. Based on a laboratory source, they developed a low-dose phase-contrast system for mammography. Their XPCI technique, using both positive and negative refracted X-rays, allows the quantitative reconstruction of absorption and phase-contrast images. The low-dose system developed and discussed in their paper was sensitive only to the negative refracted X-rays. Thus, only negative phase peaks could be determined, but the dose was decreased. This configuration allowed the visualization of fibrous structures much better than absorption and at clinically acceptable radiation doses of 0.7 to 3.0 mGy. Applications of this technique to mammography require much more study of CNRs, SNRs, evaluation of significant numbers of breast tissue samples, and development of image processing algorithms.

The simplest form of XPCI discussed above is not capable of generating DF images. Endrizzi et al. (2014) developed an EI system with appropriate masks that allows the reconstruction of all three images: absorption, differential phase-contrast, and dark field. Along with quantitative analysis of phantoms, they showed the enhancement in visibility of micro-calcifications with the DF images.
images. This technique is very robust against vibrations, and can be used with an incoherent white beam laboratory source. A study of edge enhanced X-ray phase-contrast imaging for mammography has been carried out at the Elettra synchrotron by Longo et al. (2015). The aim of the experiment was to study images of breast tissue at clinical doses using algorithms developed by Munro et al. (2013) to quantify the absorption and DPC images. They worked at energies of 17, 20, and 23 keV for optimization of the image quality. The retrieved absorption image, which contains some additional contrast due to SAXS rejection (Chapman et al. 1997), is easily interpreted by radiologists, whereas the DPC image is difficult to use for diagnostic evaluation. However, the DPC images are particularly useful for imaging sharp edges and small structures.

## 51.4 Conclusion

Phase-contrast imaging applied to mammography is in its early stages of development. As shown in this chapter, there are a number of technologies that are being used in fundamental experimental work utilizing standard laboratory, clinical, synchrotron, and new compact sources. PBI, ABI, GI, and EI all show promise as potential clinical modalities, although each one has advantages and disadvantages. The research to date has almost exclusively been proof-of-principle experiments, which have demonstrated the clear advantages of X-ray PCM over conventional absorption imaging: increased visualization of microcalcifications and tumor morphology. Image reconstruction and means of providing useful images to clinicians now allows the enhanced information to be clinically available. These early experiments have in general been done at radiation doses much larger than clinically allowed, but some recent work has been done at low doses with promising outcomes. The only clinical work to date is the PBI imaging of human patients at the Elettra synchrotron. As the research now is being directed at the use of clinical and new compact sources, it has become clear that phase-contrast imaging is also applicable and complementary to the growing use of tomosynthesis and CT as a clinical modality. The development of new compact sources and adaptation of phase-contrast methods using clinical sources should provide a very promising platform for the introduction of X-ray PCM into the clinic. Ultimately the clinical development will depend on the demand for the technologies and enhanced imaging information by practicing clinicians.

## REFERENCES


