X-ray Phase-Contrast Imaging at a Compact Laser-Driven Synchrotron Source

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Abstract

Compact laser-based X-ray sources have the potential to bridge the large performance gap between synchrotrons and conventional X-ray tube sources. One such example is the Compact Light Source (CLS), a laser-driven small-size synchrotron developed by Lyncean Technologies Inc., which produces X-rays at the intersection point of counter-propagating laser and electron beam in the process of inverse Compton scattering. In this thesis the intrinsic monochromaticity and coherence of the produced X-rays is exploited in a series of grating-based phase-contrast imaging (GBI) experiments. The grating interferometer provides information on the phase shift and the local scattering power (termed dark-field signal) of the sample under investigation, which yields soft-tissue contrast and microstructural information inaccessible in conventional X-ray imaging. The application of GBI in the context of pulmonary emphysema and breast-tumor imaging constitute the two main results of this thesis.

In early stages of pulmonary emphysema, the change in X-ray attenuation is not detectable with absorption-based radiography. Therefore, we combined the absorption-based image with the dark-field signal, which is strongly related to mean alveolar sizes in the lung. This approach allows for the discrimination between healthy and emphysematous lung tissue in a mouse model. The results were published in Schleede et al., Emphysema diagnosis using X-ray dark-field imaging at a laser-driven compact synchrotron light source, Proceedings of the National Academy of Sciences of the United States of America (2012).

In breast imaging we address two major drawbacks of mammography, namely limited attenuation contrast and glandular tissue overlap. Dose-compatible multimodal projections of a mammography phantom demonstrate an increase in contrast attainable through differential phase and dark-field imaging over conventional attenuation-based projections. The results were published in Schleede et al., Multimodal hard X-ray imaging of a mammography phantom at a compact synchrotron light source, Journal of Synchrotron Radiation (2012). Furthermore, the combination of GBI with tomosynthesis demonstrated a gain in diagnostically relevant information in fixated breast tissue both in synchrotron benchmark experiments and in dose-compatible measurements at the CLS.

At the end of this thesis, an outlook to X-ray sources that are solely built on laser technology is given with the presentation of the first phase-contrast micro-tomogram recorded at a laser-plasma betatron source.

As a result of the present work, the CLS is considered to have a strong potential of complementing conventional synchrotron sources in monochromatic high performance imaging experiments. New applications of grating-based imaging that have shown to significantly profit from the use of the technique, are pulmonary emphysema imaging and breast tomosynthesis.
Zusammenfassung


Im Ergebnis wurde in dieser Arbeit gezeigt, dass kompakte, lasergetriebene Quellen in brillanten, monochromatischen Experimenten komplementär zu konventionellen Synchrotronquellen sind. Die Lungenemphysemen-Diagnostik und die Brust-Tomosynthese sind neue Anwendungen des gitterbasierten Phasenkontrastes, die deutlich von dessen Nutzung profitieren.
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1. Introduction

In this chapter the main topic of this PhD thesis is briefly introduced in the context of research developments in the field. Section 1.2 presents the outline of this thesis.

1.1. Motivation

Very rapidly after their first invention in 1895, X-rays have found widespread use in industry, chemistry, biology, medical sciences, and research. This is due to their ability to penetrate opaque matter and their short wavelength in the angstrom range, which allows to resolve structures on an atomic scale. X-ray imaging profits from methodological developments such as phase-contrast imaging as well as from an improvement of X-ray source properties. In the work presented in this thesis we have made use of both, novel phase-contrast imaging methods and recently developed X-ray sources, which is why the two will be motivated shortly in the following.

The brilliance of X-ray sources is the main parameter used to indicate how many monochromatic and collimated photons are available in the x-ray beam. In general, all X-ray imaging experiments can be considered to be brilliance limited. Clinical imaging, which is routinely performed with polychromatic X-ray tubes, significantly profits from the use of higher brilliance sources through a reduction of exposure time, reduction of beam hardening artifacts, lower dose, and reduced blurring from extended source sizes. Unlike absorption-based X-ray imaging techniques, most coherent imaging procedures become impractical in a laboratory setting, as the required angular and spectral filtering of X-ray tube spectra results in significantly reduced flux. Examples include high resolution X-ray ptychography studies (Dierolf et al., 2010) and time-resolved diffraction experiments (Schotte et al., 2003).

Third generation synchrotron sources meet the above requirements of high average brilliance, which is as much as ten orders of magnitude higher than available from X-ray tube sources. Even higher peak-brilliance demands are met by extremely short pulses from free electron lasers (FELs)—the fourth generation of synchrotron sources. These femtosecond high intensity pulses can be used in the determination of protein structures, which can not be crystallized to larger sizes and are therefore not compatible with standard crystallography approaches. The intensity supplied in these short pulses results in the destruction of the sample and imaging of the former is only possible due to the fact that it is performed on a shorter timescale, i.e. just before the molecule is damaged (Chapman et al., 2011).

Synchrotron sources and FELs are unique in terms of radiation quality they provide but due to their high costs and large size only few exist worldwide resulting in limited access and a user demand, which by far outreaches capacities.

Thus arises the need for compact high brilliance sources both for imaging applications,
which demand a high average brilliance, and for the study of ultrafast processes requiring short X-ray pulses with a high peak brilliance. Different concepts of compact X-ray generation have been realized to fill the performance gap between synchrotrons and conventional lab sources, mostly in view of specific application’s needs.

This thesis is focussed on first experiments at compact laser-driven X-ray sources in which conventional accelerator technology is partly or fully replaced by advanced laser technology. One such example is the Compact light source (CLS), which comprises a small (few meters circumference) electron storage ring coupled to an IR-cavity, which serves as a laser undulator. In inverse Compton scattering of an electron bunch and a photon pulse hard X-rays are created with a brilliance exceeding values of conventional laboratory sources by orders of magnitude. The second laser-based source used is a betatron laser-plasma source, which uses a laser both for the linear acceleration and for the wiggling of electrons and thus constitutes one of the first available all-optical sources for hard X-rays.

In addition to serving user demand for experiments employing well established procedures, the development of new X-ray imaging techniques is largely triggered by the excellent beam properties available from synchrotron research facilities and a broader access to high brilliance sources might lead to the development of yet unforeseen experimental possibilities. One such example is grating-based phase-contrast imaging—the main imaging technique used in this thesis—, which was pioneered at synchrotron sources. Impressive benchmark soft-tissue imaging results led to the quest for a realization with a laboratory source: the Talbot-Lau-interferometer (Pfeiffer et al., 2006).

The driving force behind the use of phase contrast rather than absorption contrast in X-ray imaging is the fact that absorption-based X-ray imaging suffers from limited soft-tissue contrast, which hinders the detection of tumors. Phase-contrast imaging allows for the measurement of X-ray refraction in tissue and has proven to yield significantly enhanced soft-tissue contrast (Sztrókay et al., 2013; Tapfer et al., 2013).

The aim of this thesis is the conduction of a series of first biomedical imaging experiments at compact laser-based sources. First, we seek to validate the benefits of using high brilliance sources by studying the performance of the CLS in monochromatic CT and grating-based phase-contrast experiments. The small source size offered by a laser-plasma betatron source is exploited in the recording of a propagation-based phase-contrast CT scan.

Secondly, as the energy range and field of view currently supplied by the CLS perfectly matches the demands of mammography, a series of breast imaging experiments with mammography phantoms and breast tissue samples aims at reproducing synchrotron benchmark results and validating an increase in diagnostically relevant information under dose compatible conditions.

Thirdly, yet unresolved radiological questions, which benefit from the additional information provided in grating-based imaging, are identified. Examples where we demonstrated an increase in diagnostically relevant information through the use of grating-based imaging, comprise dark-field imaging of mouse lungs for the diagnosis of pulmonary emphysema and the transfer of absorption-based breast tomosynthesis to grating-based phase-contrast tomosynthesis.
Chapter 1. Introduction

1.2. Outline

This thesis is outlined as follows. In chapter 2 the working principles of conventional laboratory and synchrotron radiation sources are reviewed. Subsequently, an overview over recently developed laser-based X-ray sources is presented with a focus on the source concepts used in this thesis: (1) inverse Compton sources (see section 2.4.2); the Compact Light Source (see section 2.4.3); (2) laser-plasma betatron sources (see section 2.4.4).

Chapter 3 is devoted to the introduction of the principles of X-ray imaging and provides the foundation necessary for the understanding of different phase-contrast imaging techniques, which are discussed thereafter. The imaging approaches used in this thesis, namely propagation-based imaging and grating-based imaging are described in more detail in section 3.4 and 3.5 respectively. The chapter concludes with a short introduction to the concept of computed tomography (CT).

Chapter 4 is dedicated to the introduction of the experimental setup used to record the majority of the results presented in this thesis: the grating interferometer at the CLS. Advances in data processing, namely an iterative algorithm for the integration of differential phase-contrast projections is introduced and evaluated in the context of breast-tissue projection images and CT-artifact reduction in chapter 5.

Chapters 6 to 9 present the main experimental results obtained within this PhD work: In chapter 6 dark-field imaging results of emphysematous versus healthy lung tissue are presented together with a multimodal visualization of grating-based projection images, which yield the regional distribution of the disease.

In chapter 7 we present a comparison of monochromatic absorption-based CT versus polychromatic CT with a significant reduction of beam hardening artifacts obtained in the CLS scans. Multimodal grating-based CT measurements from the CLS prove both the accuracy of the technique in the measurement of a fluid phantom as well as superior soft-tissue contrast in a mouse CT scan.

In chapter 8 we present multimodal mammography phantom and breast tomosynthesis measurements from the CLS indicating an increase in diagnostically relevant information through the use of phase and dark-field images in addition to the absorption signal. The CLS tomosynthesis results are compared to synchrotron benchmark experiments obtained at beamline ID19, ESRF.

The results part concludes with an imaging experiment performed at an all-optical X-ray source, namely a propagation-based phase-contrast CT scan from a laser-driven betatron-plasma source, which is presented in chapter 9.

In chapter 10 the main scientific results are summarized and evaluated with respect to future applications and research perspectives.
Part I.

Theoretical background
Chapter 2. X-ray source technology

Electromagnetic waves are generated when electrons are accelerated by electric or magnetic fields. Between different X-ray source types from conventional X-ray tubes, over synchrotrons to the free electron laser (FEL) and compact sources, the quality of generated X-rays differs significantly, which is why demanding experiments require the use of specific source types. Not only X-ray properties vary but also the way in which the electron-accelerating fields are generated. This chapter is intended to introduce the X-ray source types used in this thesis and to compare them to well-established sources as well as to ongoing research developments in the field.

The chapter is structured as follows: In section 2.1 we introduce the parameters of brilliance, emittance, and coherence, which are used to characterize and compare the quality of X-rays from different sources. Section 2.2 covers the generation of X-rays from electrons that hit solid or fluid targets, especially the X-ray tube—the most common lab source—is introduced. An overview on first to third generation synchrotron sources is given in section 2.3. Subsequently, synchrotron sources that employ lasers for the acceleration of electrons are introduced (section 2.4). The concept of inverse Compton scattering is studied in more detail in section 2.4.2, followed by a description of the CLS in section 2.4.3. Electron acceleration in a laser-generated plasma is discussed in section 2.4.4.

2.1. Figures of merit

In order to compare different X-ray sources and to allow for an informed decision for a certain source type in view of a given experiment, there exist commonly used figures of merit to describe the quality of the emitted X-ray beam. The concepts of source brilliance, emittance and coherence will be introduced in the following. Please note that depending on the experimental task at hand, the relevant figure of merit differs. One example are time-resolved pump-and-probe experiments, which rely on high X-ray flux delivered within a short time corresponding to a high peak brilliance. CT-imaging experiments on the other hand benefit from high average brilliance resulting in a shorter measurement time. As certain source types are developed in view of specific applications, performance parameters are not always given in comparable regimes. In this chapter we will give respective numbers directly as reported in the literature.

2.1.1. Brilliance

The brilliance, $B$, relates the total X-ray flux $\Phi = N_{\text{ph}}/s$, given in number of photons $N_{\text{ph}}$ emitted per second, to how this flux is distributed in terms of X-ray energies, space
2.1. Figures of merit

and angular divergence. It is defined as the flux $\Phi$ per source area and source opening angle normalized to 0.1% energy bandwidth (Willmott, 2011):

$$B = \frac{\text{photons/second}}{\text{(mrad}^2\text{)}(\text{mm}^2 \text{source area})(0.1\% \text{ bandwidth})}$$ (2.1)

Brilliance is one of the key parameters of today’s X-ray sources as it indicates how efficiently a beam can be monochromatized and focused to a small spot. It is therefore important in all X-ray microscopy applications. The brilliance $B$ can be increased through a reduction in source size and divergence and an increase in monochromatic X-ray flux.

2.1.2. Emittance

The product of source size $\sigma$ and source divergence at a waist $\sigma_\theta$ along one dimension is known as beam emittance $\epsilon$ (Paganin, 2006), which is here defined along cartesian axes $x$ and $y$, perpendicular to the direction of propagation:

$$\epsilon_x = \sigma_x \sigma_{\theta_x}$$ (2.2)

$$\epsilon_y = \sigma_y \sigma_{\theta_y}$$ (2.3)

$\sigma$ is equal to the standard deviation (also termed rms, and related to the full width at half maximum of the beam by: $FWHM = 2\sqrt{2\ln2} \sigma$) of a Gaussian beam profile. As can be seen in the denominator of equation 2.1 a high brilliance source is characterized by a low emittance.

The concept of emittance is also used in order to describe the phase space spread of an electron beam in a storage ring or accelerator. This electron-beam parameter is important, as the generated X-ray beam inherits certain characteristics of electron-beam emittance (compare section 2.4.2).

One example for a phase-contrast imaging technique relying on parallel, monochromatic beams and thus a low-emittance high-brilliance source is analyzer-based phase-contrast imaging introduced in section 3.2.

2.1.3. Coherence

A perfectly coherent source is defined as a point source radiating over infinite time, i.e. being monochromatic with zero bandwidth. In reality such a source does not exist and real sources are often described as a superposition of a number of point sources. If these point sources radiate in phase, a source is said to be intrinsically coherent. This is realized in visible-light lasers relying on atomic transitions and free-electron lasers in the X-ray regime.

If these point sources emit waves with a random phase distribution the radiation is said to be incoherent; examples include the light bulb and a conventional X-ray tube.

In order to use these sources in imaging experiments that rely on interference effects, partial coherence is created by using apertures, monochromators or by moving sufficiently far away from the source. Coherence lengths are used to give an upper limit
on the distance by which two points may be separated that are to produce interference effects.

The longitudinal (or temporal) coherence length $l_t$ is related to the spectral bandwidth of the source (or X-ray optics) and describes the distance at which X-rays with a certain X-ray wavelength spread $\Delta \lambda$ are out of phase (have a phase offset of $\pi$) (Als-Nielsen and McMorrow, 2011):

$$ l_t = \frac{\lambda^2}{2\Delta \lambda}. \quad (2.4) $$

The transverse (or spatial) coherence length $l_s$ is related to the finite X-ray source size and angular divergence (Als-Nielsen and McMorrow, 2011):

$$ l_s = \frac{\lambda l}{2\sigma}, \quad (2.5) $$

where $\sigma$ corresponds to the source size and $l$ to the distance from the point of observation.

Examples for imaging techniques that require a high degree of spatial coherence are propagation-based phase contrast and grating-based phase contrast described in section 3.4 and 3.5, where the latter can be used with extended sources in the combination with a source grating that creates a set of line sources fulfilling the requirements for spatial coherence (Pfeiffer et al., 2006).

### 2.2. Target-based sources

In this chapter we discuss X-ray sources in which photons are generated by the deceleration of electrons in target materials. First, the most commonly used X-ray tubes are introduced in section 2.2.1; followed by a notion of new developments including fluid metal-jet targets and the combination of electron-beam storage rings with thin solid targets in section 2.2.2 and 2.2.3 respectively.

#### 2.2.1. Fixed anode and rotating anode X-ray tube

After Röntgen’s discovery of X-rays in 1895 with a so-called Geisler discharge tube, the first X-ray tube employing a heated filament and electrons accelerated to a water cooled metal target was introduced in 1912 by W.D. Coolidge. Since the 1960s cooled rotating anode X-ray tubes are used due to their increased X-ray flux. Today the X-ray tube has found widespread use in medical imaging, industrial applications and research.

Important X-ray tube parameters with respect to medical applications are a small source size to reduce blurring effects as well as high flux to yield short exposure times. In the following we will discuss the trade-off between these parameters in the context of today’s standard rotating anode X-ray tube.

In an X-ray tube electrons are emitted from a glowing filament and subsequently accelerated by a high voltage towards a target (see Fig. 2.1 (a)). When the electrons are decelerated in the passage of multiple atoms in the target material, a broad spectrum—the so-called Bremsstrahlung—is emitted. The cut-off energy of the emitted X-rays $E_c$
2.2. Target-based sources

Figure 2.1.: (a) Rotating anode schematic. Typical anode materials used for medical applications are a tungsten-rhenium target on a molybdenum core, which is backed with graphite for improved heat transfer (Dössel, 2000). The line focus principle allows for a large electron spot on the anode with a significantly smaller X-ray source size, when viewed under a certain angle. (b) X-ray tube spectrum from a tungsten anode at 120 kVp, obtained from the software XOP (Sánchez del Rio and Dejus, 2004).

is equal to the maximum kinetic energy $K = e \cdot V$ of the electrons, which is determined by the tube acceleration voltage setting $V$. The conversion efficiency of electron energy to X-rays is low ($< 1\%$) and scales with the atomic number $Z$ of the target material. As most of the electron energy is transferred into heat, target materials need to have a high melting point and a good heat dissipation, which renders tungsten as one of the most suitable target materials.

Overlaid on the continuous Bremsstrahlung spectrum, characteristic lines appear with a significantly higher intensity (see Fig. 2.1 (b)). These fluorescent X-rays are generated when an anode atom relaxes to its ground state after a core shell electron was excited. One example, where this characteristic emission is used for medical imaging is mammography with Mo as a target material with a characteristic line, $K_\alpha$, at 17 keV (Thompson et al., 2009).

In terms of brilliance, the fixed anode X-ray tube supplies $B = 10^7 - 10^8$ photons$^{-1}$ mm$^{-2}$ mrad$^{-2}$ per 0.1% bandwidth, if the characteristic lines are considered and can be utilized in experiments where monochromatic radiation is required. The continuous bremsstrahlung spectrum is two to three orders lower in magnitude. However, the X-ray energy from characteristic lines is fixed through the choice of target material and can not be tuned to a specific value suitable for the material contrast under investigation. This can be achieved with synchrotron sources as we will discuss in section 2.3.

An increase in brightness from X-ray tubes is difficult as both a decrease in electron impact spot size as well as an increase in electron-beam power density lead to additional heat load on the anode material. In addition to anode cooling and the use of base anode materials with high heat conductivity (see graphite block in Fig. 2.1 (a)), a rotating anode is used to distribute heat on the target material and keep a fixed source spot. Rotating anode X-ray tubes gain an order of magnitude in brightness as compared to fixed anode X-ray tubes.

Grating-based phase-contrast imaging (compare section 3.5) is generally perceived as
one of the most promising phase-contrast imaging techniques with respect to clinical applications. This is due to its toleration of polychromatic spectra and extended sources as provided by the conventional rotating anode.

Microfocus tubes employ electron focusing to achieve small—below 10 µm—electron impact spot sizes on the anode material at the expense of lower output power due to thermal limitations. In order to realize higher flux from a small source spot, liquid-metal jet microfocus tubes have been developed in the last years. They are introduced in the following section.

### 2.2.2. Metal-jet X-ray sources

As an alternative to a solid target material, liquid metal jets can be used as an anode in a microfocus X-ray tube. Metal alloys are employed due of their high electric conductivity, high heat load capability, and high atomic number Z. Electrons from an electron gun are focused to a small spot on a liquid metal jet with a diameter on the order of 100 µm. Using a regenerative anode in the form of liquid metal has several advantages including: higher flow speed in a stable metal jet as compared to maximum rotation speed of a rotating anode, and the fact that regenerative target materials have higher heat load capacity.

A first realization of this source type employing a Sn - Pb alloy with an X-ray spot size of 75 µm and characteristic emission of Pb around 10 keV and Sn around 25 keV is presented in Hemberg et al. (2003), where the high melting point of the alloy does not allow for continuous operation. A continuous 10 keV source employing an alloy that is liquid at room temperature and features a 7 µm FWHM X-ray spot is commercially available from Excillum AB (Kista, Sweden). In Larsson et al. (2011) a liquid-indium/gallium jet is used to generate emission of the In $K_\alpha$-line at 24 keV with a heated anode to allow for continuous operation. A peak spectral brightness of $3 \times 10^9$ photons s$^{-1}$ mm$^{-2}$ mrad$^{-2}$ per 0.1% bandwidth was reported. Due to their excellent spatial coherence properties metal-jet sources have been successfully used in propagation-based phase-contrast imaging (Lundström et al., 2012) and grating-based imaging (Thüring et al., 2013). Laser-plasma sources that use liquid jets to produce deep UV and soft X-rays in the water window are briefly discussed in section 2.4.

### 2.2.3. Thin target synchrotron combination

As opposed to thick targets where the electron is likely to interact with multiple atoms and is fully decelerated in the target material, thin targets can be passaged by electrons repeatedly (Yamada, 1996). This concept is employed in the combination of a low energy electron storage ring (6 MeV, 15 cm electron orbit diameter) and small diameter ~10-40 µm targets. The opening angle of the emitted X-rays is given by the kinetic energy of the electrons ($1/\gamma = 85$ mrad, compare section 2.3) and the resulting spectrum is highly polychromatic ranging from 1 keV to 6 MeV. The spectrum can only be tuned through changes in target material. Up to date this source type has been realized with 4, 6 and 20 MeV electron energy (Yamada et al., 2006). The small source size, which is defined by the small size of the target has been studied in the context of propagation-based phase-contrast imaging (Hirai et al., 2006). We have not further investigated this source
concept as high X-ray energies of up to 6 MeV are disadvantageous in medical imaging applications.

2.3. Synchrotron sources

Synchrotron radiation is defined as electromagnetic radiation emitted by relativistic charged particles that are forced on curved trajectories. The outstanding properties of synchrotron radiation include high brilliance, a high degree of collimation, tunable X-ray wavelength, a highly polarized beam and its time structure. The combination of these properties render synchrotron radiation facilities unique for a large range of experiments. In the following we will discuss the basics of synchrotron radiation in terms of emitted X-ray beam properties.

In contrast to the dipole radiation emitted by an electron that is moving at small speed compared to the speed of light, electrons that are traveling at relativistic speed emit radiation into a narrow cone of half-angle \( \theta \approx 1/\gamma = \sqrt{1-v^2/c^2} \), which is pointing in the traveling direction of the electron. For electrons moving on a circular path radiation is thus strongly confined in the tangential direction. Its shape is often referred to as that of a sweeping search light (compare red cone in Fig. 2.2 (a)). This cone angle can be derived from a Lorentz transform of the angular distribution of dipole radiation in the electron rest frame to the laboratory frame. The intensity of radiation has its maximum along the traveling direction of the electron and falls off by a factor of two when the electron is viewed under an angle of \( \pm 1/\gamma \) by the observer. The Lorentz factor \( \gamma = E_e/m_0c^2 \) is equal to the ratio of electron energy to its rest mass energy, meaning that the higher the electron energy the narrower the radiation cone. The opening angle originating from 1 GeV electrons is on the order of 0.5 mrad (Willmott, 2011).

In first generation synchrotron sources, namely accelerators built for particle physics experiments, synchrotron radiation was generally perceived as a by-product that limited the maximum achievable particle energy due to radiation losses. Synchrotron radiation in the visible part of the electromagnetic spectrum was first reported by Elder et al. (1947).

Second generation machines were solely built for and dedicated to the production of synchrotron radiation. After being accelerated to the desired energy, electrons are stored at a fixed energy in a storage ring. These rings comprise alternating straight sections, in which electrons are focused and reaccelerated using radio-frequency cavities to account for radiation losses, and bending magnets (see Figure 2.2 (a)), which force electrons on a circular path. In second generation synchrotrons these bending magnets constitute the primary source of radiation. An electron that enters the homogeneous magnetic field of a bending magnet is deflected due to the Lorentz force. The wavelength of the emitted radiation ranges from the IR to the X-ray regime due to a Doppler shift of the orbital frequency \( \omega_0 \) of the electron in the ring. The critical or characteristic frequency \( \omega_c \) of the emitted spectrum can be calculated from the pulse duration \( \Delta t = 1/(\gamma \omega_0) \) during which the electron traverses an arc of \( 1/\gamma \) and the time compression experienced
Figure 2.2.: (a) Bending magnet schematic. (b) Calculated spectrum from a bending magnet. (c) Permanent magnet undulator. (d) Schematic (low $K$) undulator spectrum (d), adapted from Als-Nielsen and McMorrow (2011). The number of the harmonics in the undulator spectrum as well as their relative strength depend on the undulator parameter $K$. 
by the observer due to the Doppler effect \( \sim 1/\gamma^2 \) (Als-Nielsen and McMorrow, 2011):

\[
\omega_c = \frac{3}{2} \gamma^3 \omega_0 = \frac{3}{2} \gamma^3 \frac{c}{R},
\]

(2.6)

with the trajectory radius of curvature \( R \) and the angular orbital frequency of the electron in the storage ring of \( \omega_0 \). In units of magnetic flux density \( B_0 \) and electron energy \( E_e \), the critical energy of the spectrum can be expressed as (Als-Nielsen and McMorrow, 2011):

\[
h\omega_c [\text{keV}] = 0.665 E_e^2 [\text{GeV}] B_0 [\text{T}] .
\]

(2.7)

As the magnetic flux densities in bending magnets are limited to \( \sim 1 \text{T} \) in permanent magnets and \( \sim 5 \text{T} \) in superconducting magnets, electron energies have to be in the GeV range to generate hard X-rays. The maximum achievable magnetic flux density \( B_0 \) also determines the bend radius \( R \) for relativistic electrons of energy \( E_e \) in a storage ring:

\[
R [\text{m}] = 3.3 E_e [\text{GeV}] / B_0 [\text{T}] \quad \text{(Als-Nielsen and McMorrow, 2011)}
\]

and thus accounts for the large size of high energy storage rings.

The spectrum from a bending magnet source in the horizontal plane can be calculated from modified Bessel functions \( K_{2/3} \) and depends on the ratio of emitted X-ray energy and critical energy (Als-Nielsen and McMorrow, 2011):

\[
\frac{\text{photons/second}}{\text{mrad}^2 0.1\% \text{BW}} = 1.33 \times 10^{13} E_e^2 [\text{GeV}] I [\text{A}] (\omega/\omega_c)^2 K_{2/3}^2 (\omega/\omega_c).
\]

(2.8)

A bending magnet spectrum calculated with the formula above is shown in Fig. 2.2 (b). The shape of this spectrum is comparable to the spectrum from a wiggler (discussed below) and the broad spectrum emitted by a betatron laser-plasma source, which will be discussed in section 9.3.

In the horizontal plane, the fan angle from a bending magnet is larger than the natural opening angle of \( 1/\gamma \) as indicated in Fig. 2.2 (a). It is equal to the angular range traversed by electrons (as seen by an observer in the laboratory frame) plus the opening angle cone itself. Brilliances on the order of \( 10^{15} \) photons s\(^{-1}\) mm\(^{-2}\) mrad\(^{-2}\) per 0.1\% bandwidth are achieved with bending magnets. These sources are useful in experiments, where a lot of polychromatic flux in a large field of view is needed; one example being CT scans of large samples and experiments which use UV photons or soft X-rays.

One characteristic of third generation synchrotron sources is the use of insertion devices as the main source of synchrotron radiation. In these insertion devices—inserted into straight sections of the storage ring—periodic alternating magnetic structures force the electrons on a nearly sinusoidal path in the plane of the storage ring (see Figure 2.2 (c)). The degree to which an electron deviates from a straight trajectory is used to differentiate between two types of insertion devices, which emit considerably different X-ray spectra: if the angular deviation exceeds the natural opening half angle of \( 1/\gamma \), there is no significant overlap from radiation emitted at each turn along the sinusoidal path and the device is termed wiggler; otherwise cones emitted at consecutive turns overlap and interfere. In this case the device is called undulator.

The maximum angular deviation from a straight path \( \phi_{\text{max}} \) defines the parameter \( K = \phi_{\text{max}} \gamma \), which is used to distinguish the undulator regime, \( K \approx 1 \), from the wiggler
Chapter 2. X-ray source technology

regime $K \sim 10 - 20$ (Willmott, 2011). The undulator (or wiggler) parameter $K$ can be calculated from the maximum magnetic flux density $B_0$ and the magnetic field period $\lambda_u$ (Als-Nielsen and McMorrow, 2011):

$$K = \frac{eB_0\lambda_u}{2\pi m_0c} = 0.934 \lambda_u [cm] B_0 [T].$$

(2.9)

**Wiggler**

Wigglers are characterized by a rather strong magnetic flux density $B_0$ forcing the electrons to perform large amplitude oscillations in the magnetic structure. Radiation cones show significant overlap only along the center of the structure. Radiation is added incoherently, resulting in a bending-magnet like spectrum (see Fig. 2.2 (b)) with an emitted intensity that is proportional to the number of wiggler periods $N$. Brilliances on the order of $10^{16} - 10^{17}$ photons s$^{-1}$ mm$^{-2}$ mrad$^{-2}$ per 0.1% bandwidth are achieved at wiggler beamlines. The horizontal opening angle is proportional to $\gamma^{-1}$, namely $\theta_h = 2K/\gamma$ and thus larger for wigglers as compared to undulators.

**Undulator**

In an undulator, radiation cones emitted from one electron at different positions in the undulator overlap due to the smaller deviation of the electrons from a straight path. When the condition for interference is met—the wavelength of the emitted radiation corresponds to a harmonic of the undulator—radiation is added coherently and spikes appear in the spectrum (see schematic undulator spectrum Fig. 2.2 (d)). In contrast to the free-electron laser, which is described in the following, radiation from different electrons is added incoherently as they do not exhibit a fixed phase relationship. Undulators have brilliance values on the order of $10^{18} - 10^{19}$ photons s$^{-1}$ mm$^{-2}$ mrad$^{-2}$ per 0.1% bandwidth, corresponding to an increase by ten orders of magnitude compared to rotating anode X-ray tubes. The fundamental wavelength $\lambda_1$ of an undulator can be derived from the condition for constructive interference, namely by setting $n\lambda_1$ (with $n = 1$ for the fundamental wavelength) equal to the phase difference from two consecutive points of emission, $c\Delta t - \lambda_u$, which results in (Willmott, 2011):

$$\lambda_1 (\theta) = \frac{\lambda_u}{2\gamma^2} \left( 1 + \frac{K^2}{2} + (\gamma\theta)^2 \right).$$

(2.10)

By setting the observation angle $\theta = 0$, the on-axis emitted radiation from an undulator can be calculated. Thus, with an undulator period that is typically on the order of cm, the relative electron energy $\gamma$ has to be on the order of $10^4$ for the fundamental wavelength to be within the angstrom range. The spectrum can be tuned by varying the undulator gap, corresponding to a change in $K$ via the magnetic flux density $B_0$ (compare equation 2.9). Furthermore, the relative strength of the harmonics with respect to the fundamental undulator wavelength is increased by increasing $K$ (Als-Nielsen and McMorrow, 2011). The bandwidth of an undulator harmonic is described by $\Delta\omega/\omega_n \approx 1/(nN)$, corresponding to a smaller bandwidth when using a large number of periods $N$ and a high undulator harmonic $n$. The opening angle of undulator radiation is approximately symmetric in horizontal and vertical direction: $1/(\gamma\sqrt{N})$. 
Please note that in the electron frame the passage of an undulator—a varying magnetic field orthogonal to the electron traveling direction—corresponds to a counter propagating plane electromagnetic wave (Bilderback et al., 2005). This analogy is exploited in the Compact Light Source (CLS), which is introduced in section 2.4.3. At the CLS a counter propagating laser pulse replaces the static magnetic structure of a conventional undulator.

The free electron laser (FEL) constitutes the fourth generation of synchrotron sources with enhanced X-ray properties including an intrinsically coherent beam, short pulses below 100 fs, and peak brilliances on the order of $10^{32}$ (Als-Nielsen and McMorrow, 2011).

The coherent emission of photons is based on micro bunching of electrons, which can be induced in several hundred meters long undulators with low emittance electron beams. The coherent emission of X-rays is based on the fact that point-like charges emit light coherently; here point-like corresponds to a charge distribution in the order of or smaller than the emitted radiation wavelength. Electron bunches in synchrotrons are significantly larger than the radiated wavelength and radiation from different electrons in a conventional undulator thus adds incoherently, i.e. not in phase, whereas micro bunches in an FEL are small enough to emit in phase. Micro-bunches in an FEL are generated if the electron emittance is sufficiently small and the electron bunch not only experiences the external fields from the undulator but also the radiation field from the emitted X-rays. In the electron frame the counter propagating wave from the undulator field interferes with the wave emitted by the electron itself (self amplified spontaneous emission (SASE)) and forms a standing wave pattern with the periodicity of the undulator fundamental wavelength $\lambda_1$. Therefore, the large electron cloud is transformed to small micro bunches of $N_q$ electrons, which emit coherent X-rays. Coherent addition results in an intensity boost by $N_q^2$ (incoherent radiation scales with $N_q$), which yields highest peak brilliances among X-ray sources. The short pulse lengths provided by FELs can be exploited in studies of atomic motions in matter ($\sim$ps to $\sim$fs time scale), which are inaccessible with synchrotron pulses ($\sim 50$ ps) (Willmott, 2011). The coherence of the X-ray laser can be exploited in all experiments that rely on interference effects.
2.4. Laser-driven X-ray sources

As indicated in the previous section, the possibilities for size and cost reduction of large synchrotron facilities are limited by the electromagnetic fields generated with conventional accelerator technology. In order to overcome these limitations, high intensity laser pulses can be used both for the acceleration and oscillation of electrons. Due to the generation of significantly larger electric field gradients, electrons can be accelerated to relativistic energies within a few millimeters. Laser pulses allow for electron oscillations on length scales not attainable using conventional undulators. Furthermore, laser-driven X-ray sources are capable of delivering X-ray pulses shorter than those obtained from conventional synchrotrons. Different compact laser-based sources of electron beams and X-rays have been demonstrated or are envisioned. This section is intended to provide a brief overview on laser-driven sources with a focus on the source concepts used in this thesis.

In section 2.4.1 we will give an overview over different concepts of soft to hard X-ray generation with lasers. An introduction to the principles of inverse Compton scattering is given in 2.4.2. Subsequently, a detailed description of the Compact Light Source (CLS)—the X-ray source at which most of the experiments presented in this thesis were performed—is given in section 2.4.3. Basic principles of laser-wakefield acceleration and betatron oscillations in laser-generated plasmas are given in section 2.4.4.

2.4.1. Overview

In this overview, which is based on a review by Carlsten et al. (2010), we will first discuss the use of lasers for the linear acceleration of electrons. Thereafter, the use of lasers for the generation of soft to hard X-rays is discussed. X-ray sources that use lasers for the acceleration of electrons and the production of X-rays, meaning that they operate without conventional accelerator technology, are termed all-optical sources in the following.

Electron acceleration with lasers

Electron acceleration with conventional microwave technology is limited to gradients of about 100 MeV/m (Carlsten et al., 2010). The advent of high power lasers has paved the way for electron acceleration on significantly shorter length scales:

- **Laser-driven plasmas** (or laser-plasma accelerators) are created when a high power laser is focused on a gas target. The gas is immediately ionized and accelerating gradients on the order of 10-100 GV/m are generated in the plasma. High quality 1 GeV electron bunches of 10 pC charge and with fs-bunch lengths have been reported (Carlsten et al., 2010). Electron acceleration and oscillation in laser-generated plasmas is discussed in more details in section 2.4.4. Alternatively plasma waves can be generated with electron beams; a concept, which will not be discussed in this thesis and the reader is referred to Carlsten et al. (2010) and references therein.

- **Direct laser acceleration** (DLA) of electrons in dielectric structures is currently limited to bunch charges on the order of fC (Carlsten et al., 2010). The latter
2.4. Laser-driven X-ray sources

concept is not further discussed in this thesis and the reader is referred to Lin (2001), Plettner et al. (2009), and references therein.

X-ray generation with lasers

For the generation of X-rays with lasers we differentiate between incoherent sources and intrinsically coherent beams as known from an FEL:

Incoherent X-rays are produced by:

• **Conventional undulator**: A combination of electron bunches, which are generated in a laser-induced plasma, with a short, 30 cm-long undulator featuring periods of 5 mm was used for soft X-ray generation down to wavelengths of $\lambda = 7 \text{ nm}$ with an X-ray pulse duration dominated by electron bunch length of 10 fs (Fuchs et al., 2009). To create hard X-rays either the electron energy would have to be increased or the undulator period further reduced (compare equation 2.10).

• **Betatron oscillations** in a laser generated plasma constitute an all-optical source that generates a wiggler-like spectrum with short pulse lengths on the order of fs and source sizes on the order of $\mu \text{m}$ (details are given in section 2.4.4).

• **Laser plasma radiation** can be used for the generation of extreme ultraviolet (EUV) to soft X-rays and is another example for an all-optical source. A high-intensity laser that is focused on a gas creates a plasma and raises its temperature to $\sim 100000 \text{ K}$ allowing for the emission of EUV to soft X-ray light. Different processes contribute to the emitted radiation with a domination of line emission in low atomic number targets and a combination of line emission and blackbody radiation in high atomic number targets. Examples range from X-rays with a spectrum spanning 4 to 14 keV generated with a liquid-metal gallium jet (Korn et al., 2002) to ammonium hydroxide droplets with an emission at 2.88 nm (430 eV) for water-window microscopy (Rymell et al., 1995). Line emission from tin or liquid xenon jets around 13 nm (95 eV) has been discussed as a possible source for EUV lithography due to a potentially high radiation output and continuous operation mode (Hansson and Hertz, 2004).

• **Inverse Compton scattering** offers an undulator like spectrum of X-rays. In an inverse Compton source the magnetostatic field of a conventional undulator is replaced by the electromagnetic field of a laser pulse. This results in a reduction in undulator period from cm to $\mu \text{m}$ and therefore allows for the use of lower energy electron beams (compare undulator equation 2.10, with $\lambda_u = \lambda_{\text{laser}}/2$). Due to the reduced electron energy, the size of the storage ring can be decreased significantly. Advantages of inverse Compton sources comprise a tunability in wavelength via relative electron energy $\gamma$, a small source size and a narrow on-axis X-ray spectrum.
Coherent X-rays are generated with:

- **High harmonic generation (HHG)** is often described as the compact, low-flux counterpart of the FEL. In addition to a similarity in X-ray properties, HHG is discussed in the context of FELs as a seeding option. The basic principles of HHG are presented in the following.

**High harmonic generation** is induced by focusing a few-mJ, femtosecond pulse on a noble gas. In a nonlinear process the wavelength of the laser is upconverted to higher harmonics ranging from EUV to soft X-rays. Unique properties include very short pulse lengths on the attosecond scale, intrinsic coherence, a high degree of polarization, and the fact that the emitted radiation is synchronized with the laser that drives the process itself, allowing for pump-and-probe experiments with attosecond temporal resolution.

High harmonic generation can be explained by using the semiclassical *recollision* picture, in which an atom is tunnel-ionized in the field of an ultrashort laser pulse. The freed electron is accelerated in the field of the laser and after half an optical cycle (when the direction of the field is reversed) reaccelerated towards the parent nucleus. In this reacceleration process, in which the electron recombines with the ion, a higher harmonic photon is emitted. HHG sources thus provide a spectrum with peaks ranging from UV to few-keV X-rays. The high energy cut off of the spectrum can be calculated from the average kinetic energy, $U_p$, of an electron oscillating in the laser field and the ionization potential $I_p$:

$$E_{\text{max}} = I_p + 3.17 U_p,$$

in which $U_p \propto I_L \lambda_L^2$ scales linearly with laser intensity $I_L$ (up to a saturation value) and quadratically with laser wavelength $\lambda_L$. Counter intuitively the cut off energy can be increased through an increase in laser wavelength to the mid-IR range (3.9 $\mu$m) for the generation of X-rays of more than 1.6 keV (Popmintchev et al., 2012). To gain a bright output beam, radiation from a large number of atoms has to add up coherently, meaning that the drive laser and the emitted X-rays have to travel at the same phase velocity in the medium. Similarly to the description of X-ray beam properties, a coherence length is defined over which radiation is efficiently added. The extension of efficient output of these sources to the X-ray regime has been hindered by the fact that the required higher photon intensities (compare dependency on $I_L$ in equation 2.11) result in dispersion in the strongly ionized gas medium and thus a higher phase velocity mismatch between driving laser and emitted higher harmonics.

Flux levels of $10^5$ photons per pulse in 0.1% energy bandwidth have been demonstrated (Popmintchev et al., 2012). This flux can be further increased by maximizing the interaction region, minimizing absorption in the medium, and phase matching of the fundamental and harmonic radiation over the interaction volume.

Coherent diffractive imaging using high harmonics in the range of 30 nm has been demonstrated by Chen et al. (2009).
2.4. Laser-driven X-ray sources

2.4.2. Inverse Compton sources

Unlike Compton scattering where a photon looses energy when scattered by a free electron, inverse Compton scattering of low energy photons (visible or infrared (IR)) with relativistic electrons (MeV scale) can be used to generate high-energy photons: X-rays and gamma rays. Relaxed requirements on electron energy offer the possibility to create compact inverse Compton sources that deliver synchrotron-like X-rays. This section is built on the results presented in Loewen (2003).

The section is structured as follows: First, the use of inverse Compton scattering for the generation of X-rays is motivated via the laser-undulator duality concept. Thereafter, starting from the particle-particle collision process, the spectrum of an inverse Compton source in backscattering geometry is presented. Indications for flux maximization are derived from a beam-beam interaction picture, along with the notion of different concepts of inverse Compton X-ray sources. Finally, the Compact Light Source (CLS), commercially developed and manufactured by Lyncean Technologies, Inc (Palo Alto, USA), is described in section 2.4.3.

Motivation

In short, an inverse Compton X-ray source is characterized by a synchrotron-like electron bunch at modest electron energies, which collides in a spot of tight focus with a laser pulse. Due to the modest electron energies involved in the process, the storage (or acceleration) units for the electron beam can be made rather compact ∼m-scale as compared to ∼100 m-scale for conventional storage rings (accelerators). Compared to other laser-driven sources of X-rays mentioned in the previous section, inverse Compton sources offer an undulator-like X-ray beam, which is highly collimated, tunable, highly polarized and monochromatic. The lower natural bandwidth is advantageous for X-ray optics use, as the emitted power is centered at and limited to the desired wavelength, which results in reduced heat load on optics components compared to wiggler experiments.

The spectrum originating from the head-on collision of an electron bunch with a laser pulse can be understood by using the analogy of a permanent magnet undulator and a laser-undulator concept presented in the following.

From reconsidering the equation that describes undulator radiation on axis:

\[ \lambda_1 (\theta = 0) = \frac{\lambda_u}{2 \gamma^2} (1 + K^2/2), \]  

(2.12)

it is obvious, that production of X-rays with a simultaneous decrease in relative electron energy \( \gamma \) is only possible by decreasing undulator period. In conventional undulators this period is given by the size of the permanent magnets and typically on the order of cm. One solution is the use of a laser undulator, i.e. an effective undulator that is formed by the electromagnetic wave of a counter propagating laser beam.

In a conventional undulator the relativistic electron traverses a periodically alternating static magnetic field. In the electron frame, this static magnetic field is seen as a counter
propagating electromagnetic wave. Making use of this analogy a counter propagating laser pulse—a laser undulator—can be used to produce X-rays. The resulting undulator period is in this case defined by the laser wavelength (\(\sim 1\mu\text{m}\)) and thus four orders of magnitude smaller than conventional undulator periods (\(\sim \text{cm}\)). From equation 2.12 it is obvious that the corresponding relative electron energy can be reduced by a factor of 100.

Relations between undulator parameters, i.e. period and magnetic field, to laser parameters, namely laser wavelength and intensity, can be derived from comparing the forces that cause transverse oscillations in the electron frame for both cases (Als-Nielsen and McMorrow, 2011). This is achieved by Lorentz transforming the electric and magnetic fields of the laser wave (\(E_l, B_l\)) and the undulator magnetic field (\(B_u\)) to the electron frame. Assuming the electron velocity to be close to the speed of light \(v_e \approx c\), the effective undulator period and magnetic field strength of a laser undulator are given by (Als-Nielsen and McMorrow, 2011):

\[
\lambda_u = \lambda_l/2 \\
B_u = 2B_l,
\]

with \(B_l = \frac{1}{2}\sqrt{2Z_0I}\), in which \(I\) describes laser intensity and \(Z_0 = 1/(\epsilon_0c) = 377\Omega\) is the free space impedance (Huang and Ruth, 1998). From these results it is possible to calculate the energy of the first undulator harmonic \(E_{\lambda_1} = 4\gamma^2E_l\) using equation 2.12, as well as the K parameter associated with a certain laser intensity. X-rays with an energy of \(E_e = 21\text{ keV}\) can thus be generated with electrons of \(E_e = 34\text{ MeV}\) and a laser wavelength of \(\lambda_l = 1064\text{ nm}\). Note that with a laser pulse length on the order of 25 ps the laser-undulator comprises \(N_u = 25\text{ ps}\cdot c/(\lambda_l/2) \approx 14000\) periods.

In addition to a description of inverse Compton scattering with an effective laser undulator one can employ a particle picture of the collision process to calculate the X-ray spectrum and estimate the X-ray energy and angular spread.

**Inverse Compton scattering**

Using principles of particle-particle collision we can describe inverse Compton scattering as a process in which a relativistic electron collides with a photon, transfers part of its energy, and boosts the energy of the laser photon to the X-ray regime (sketched in Fig. 2.3).

In the following, the scattering event is discussed in the laboratory frame, in which the electron initially has a of momentum \(\vec{p}\) and collides at an angle \(\theta_i\) with a laser photon of wavevector \(\vec{k}\). This photon is scattered at an angle \(\theta_f\) with respect to the electron traveling direction and its momentum is increased to \(\hbar\vec{k}'\). Considering conservation of the 4-momenta of the electron \(p = (E_e/c, \vec{p})\) and the photon \(k = (E_l/c, \hbar\vec{k})\) (Sun and Wu, 2011):

\[
p + k = p' + k',
\]

yields a relation between scattered photon energy \(E_x = E_l'\), which is depending on electron energy \(E_e\), laser photon energy \(E_l\) and scattering angles \(\theta_i\) and \(\theta_f\):

\[
E_x = \frac{(1 - \beta \cos \theta_i) E_l}{1 - \beta \cos \theta_f + E_l/E_e (1 - \cos (\theta_i - \theta_f))}
\]
2.4. Laser-driven X-ray sources

Figure 2.3.: Inverse Compton scattering in the laboratory frame. An electron of momentum $\vec{p}$ collides at an angle $\theta_i$ with a laser photon of wavevector $\vec{k}$. This photon is scattered at an angle $\theta_f$ with respect to the electron traveling direction and its momentum is increased to $\hbar \vec{k}'$. This figure is adapted from Loewen (2003).

X-ray energies associated with scattering angles from 0 to 20 mrad, a laser wavelength of $\lambda_l = 1064$ nm and an electron energy of 34.6 MeV are plotted in Fig. 2.4 (a). It follows that the spectral bandwidth can be tuned via an aperture or the angular acceptance of the imaging geometry (electron beam influences on the X-ray spectrum are discussed later in this section). The tunability of X-ray energy via changing electron energy $E_e$ is illustrated in Fig. 2.4 (b).

For a head-on collision ($\theta_i = \pi$) and on-axis observation ($\theta_f = 0$), equation 2.16 simplifies to:

$$E_x = \frac{E_e (1 + \beta)}{(1 - \beta) E_e - 2E_l} = \frac{E_e (1 + \beta)^2 E_l}{E_e/\gamma^2 - 2E_l} \approx 4\gamma^2 E_l.$$  \hspace{1cm} (2.17)

In the last steps we neglect the recoil of the electron, i.e. assuming that $E_l \ll m_0c^2$ and made use of the relation $\gamma = 1/\sqrt{1 - \beta^2}$. Please note that this result is equal to the one derived from a laser-undulator analogy in the previous section.

In the following we assume a head-on collision, i.e. $\theta_i = \pi$. From the Klein-Nishina formula, which provides the cross section for scattering in the case that the electron is at rest, one can derive the cross section for scattering in the laboratory frame (Stepanek, 1998):

$$\frac{d\sigma}{\sin \theta_f d\theta_f} = \pi r^2 \frac{1 - \beta^2}{(1 - \beta \cos \theta_f)^2} R^2 \left( R + \frac{1}{R} - 1 + \left( \frac{\cos \theta_f - \beta}{1 - \beta \cos \theta_f} \right)^2 \right),$$  \hspace{1cm} (2.18)

with $R$ being the ratio of laser photon energy and X-ray photon energy in the electron rest frame, which can be calculated from equation 2.16 by setting $\beta = 0$. The angular intensity distribution originating from the inverse Compton process, is given by the cross section $\frac{d\sigma}{\sin \theta_f d\theta_f}$ and plotted versus scattering angle $\theta_f$ in Fig. 2.4 (c). Scattered intensity decreases rapidly with increasing scattering (opening) angle $\theta_f$, but stays rather constant in the 4 mrad cone indicated by red dotted lines.

Taking the derivative of equation 2.16 with respect to $\theta_f$ and using the fact that $d\sigma/dE_x = d\sigma/d\theta_f \cdot d\theta_f/dE_x$ one obtains the differential cross section with respect to
Figure 2.4.: X-ray energy and angular spread for an electron energy of 34.6 MeV and a laser wavelength of 1064 nm. (a) X-ray energy over scattering angle $\theta_f$ for head-on collision $\theta_i = \pi$. (b) Maximum on-axis X-ray energy for electron energies in the range from 0 to 44 MeV. (c) Differential on-axis X-ray energy over scattering angle $\theta_f$. Red dotted lines indicate the $\pm 2$ mrad cutoff used at the CLS. (d) X-ray intensity over X-ray energy, calculated from equation 2.19. The red area marks X-ray photons emitted into a 4 mrad opening angle; corresponding energy levels are obtained from (a).
2.4. Laser-driven X-ray sources

Figure 2.5.: Inverse Compton scattering of two particle beams with $N_l$ photons and $N_e$ electrons that are focused to a matched waist of width $\sigma_r$. X-rays are emitted in the direction of the incoming electron.

X-ray energy (equation 2.3 in Loewen (2003)):

$$\frac{d\sigma}{dE_x} = \frac{\pi \gamma_e^2}{2} \frac{1}{\gamma^2 E_l} \left[ \frac{E_e^2}{4 \gamma^2 E_l^2} \left( \frac{E_x}{E_e - E_x} \right)^2 - \frac{E_e}{\gamma^2 E_l E_e - E_x} + \frac{E_e - E_x}{E_e} + \frac{E_e}{E_e - E_x} \right],$$

which can be used to calculate the shape of the emitted spectrum. A spectrum emitted into the full angular range, i.e. $\theta_f$ covering 0 to $\pi$, with an electron energy of $E_e = 34.6$ MeV, and a laser wavelength of 1064 nm is shown in Fig. 2.4 (d). The high-energy cut-off is defined by the electron energy and the laser wavelength. The red area indicates X-ray energies observed in a 4 mrad cone corresponding to a tunable low energy cut off, i.e. the possibility to monochromatize the beam via an aperture.

The fixed relation of emission angle $\theta_f$ and X-ray energy $E_x$ provided by equation 2.16 does not hold under experimental conditions. An X-ray energy spread $\Delta E_x/E_x$ results from uncertainties in electron energies, scattering angles and photon energy. It can be calculated from the corresponding derivatives of equation 2.16 (Sun and Wu, 2011). Approximated contributions from electron beam energy and angular spread are $2 \Delta E_e/E_e$ and $-\gamma^2 \Delta \theta_f^2$ respectively.

At the CLS, the effect of the electron energy spread is visible in a broadening of the high-energy tail of a real spectrum (compare CLS X-ray spectrum presented in Fig. 2.7). The low energy tail is further broadened by the electron beam divergence $\Delta \theta_e$. Both effects account for the natural X-ray bandwidth of 3%. The electron angular spread determines the divergence of the X-ray beam. A low emittance electron beam thus provides a low emittance X-ray beam.

**Luminosity and Flux**

In an inverse Compton source bunches of electrons and photons collide, rather than isolated single particles (compare Fig. 2.5). Thus, a beam-beam scattering view of the process can be employed to estimate parameters for overall flux optimization.

The luminosity is a commonly used concept to describe beam-beam interaction optimization. For the case of two Gaussian beams with matched sizes in the interaction
region, the total intensity $\dot{N}_x = L_0 \sigma_{\text{Th}}$ of scattered photons per time is described by the luminosity $L_0$ times the cross section of the event, which can be approximated by the cross section for Thomson scattering $\sigma_{\text{Th}}$. The Thomson cross section is used as a simplification of the total cross section for Compton scattering and is applicable if recoil effects are negligible:

$$\sigma_{\text{Th}} = \frac{8\pi}{3} r_e^2 = 6.65 \times 10^{-29} \text{m}^2, \quad (2.20)$$

in which $r_e$ corresponds to the classical electron radius. The small value of $\sigma_{\text{Th}}$ implies that obtaining high flux from this interaction process is challenging. The luminosity is defined via the number of particles in the electron and photon bunch $N_e$ and $N_l$ and the transverse spot size $\sigma_r$ (Loewen, 2003):

$$L_0 = f_c \frac{N_e N_l}{4\pi \sigma_r^2}, \quad (2.21)$$

here $f_c$ describes the collision frequency, which is an important parameter with respect to X-ray flux optimization. Furthermore, flux can be increased from an increase in electron bunch charge, $N_e$, or stored optical power in the cavity, i.e. number of photons $N_l$, and tighter focusing of the beams to a smaller interaction spot size $\sigma_r$. In order to achieve stable operation, some of these parameters can not be deliberately increased. One example is the electron bunch charge, which is limited due to increasing intrabeam-scattering effects as described in Loewen (2003).

The luminosity is useful for a comparison of different concepts of inverse Compton sources. Here we will compare systems based on linear accelerators to storage ring systems like the CLS.

Advantages of storage rings comprise a high repetition rate on the order of MHz and thus high average photon flux. On the other hand relatively long electron bunches generate long pulses of X-rays, which do not allow for time resolved experiments of processes on a fs timescale. Furthermore, a reduction of the beam spot sizes is limited by the pulse length as spot sizes much smaller than the bunch lengths lead to flux reduction due to the hourglass effect.

Linear accelerators (Linacs) generally feature a significantly lower repetition rate and thus dramatically reduced average flux, whereas enhanced electron beam emittance parameters yield smaller spot sizes at lower angular divergence as compared to a storage ring based system. Furthermore, the shorter electron bunch length can be exploited in the generation of short X-ray pulses and tighter focusing without flux reduction due to the hourglass effect. A Linac-based system generating sub picosecond pulses at a low repetition rate has been realized by Urakawa (2011). Concepts based on superconducting linacs featuring higher repetition rates, as well as the use of energy recovering linacs are proposed (Graves et al., 2009).

In addition to the backscattering geometry ($\theta_i = \pi$) employed in the above mentioned sources, 90° - inverse Compton scattering has been realized as a means for the generation of short (~ps) pulses of X-rays and gamma radiation (Kim et al., 1994; Taira et al., 2012). Short pulses are achieved at the expense of a lower energy transfer and lower luminosity compared to a backscattering geometry.
2.4.3. The Compact Light Source (CLS)

Most of the experimental results presented in this thesis have been measured at the Compact Light Source (CLS), commercially developed and manufactured by Lyncean Technologies, Inc (Palo Alto, USA). The CLS is an inverse Compton source offering synchrotron-like emission from a laboratory-scale machine. Its main components comprise an electron beam injector, a storage ring, and an optical cavity (compare CAD drawing and picture Fig. 2.6).

In the following we will shortly review the main components of the machine: A radio-frequency electron gun and a laser-driven photocathode produce single electron bunches, which are accelerated to an energy in the range of 20 to 44 MeV in a linear electron accelerator section. The linear accelerator is built of conventional high power microwave acceleration cavities. The bunch is stored at this energy in a miniature storage ring with a circumference of less than five meters (Fig. 2.6). Electron bunches circulate in a stable fashion at a frequency of 65 MHz for about million turns. They are reaccelerated with an RF cavity and the injector periodically refreshes the bunch to maintain high beam quality at a re-injection rate of 30 Hz.

A high-finesse bow-tie laser enhancement cavity is located at one of the straight sections of the storage ring and is resonantly driven by a mode-locked infrared Nd:YAG laser of wavelength $\lambda_l = 1064$ nm. Laser pulses of 25 ps and a laser power of 50 kW are built up in the cavity, which features four high reflectivity mirrors. At the interaction point the laser and the electron bunch are tightly focused to a small spot and pass through each other on each revolution of the electron bunch and each cycle of the laser pulse. Pulses of X-rays are produced from inverse Compton scattering on each revolution of the electron and laser beam (Huang and Ruth, 1998). X-rays exit the cavity through a thin region included in one of the mirrors, leading to a 4 mrad cone with nearly uniform intensity and spectrum across the beam (compare Fig 2.4 (a) and (c)). The size of the aperture is determined by fabrication feasibility, acceptable spectral bandwidth and desired field of view at a given distance of the experiment to the source.

The bunches are usually collided at approximately matched waists, where the X-ray spot size is defined by the overlap of the two beams. The electron bunch length and laser pulse length are $\sim 1.5$ cm and $\sim 1$ cm respectively. Tight focusing of both the electron bunch and the infrared laser results in high flux and a small source size on the order of $40 \times 40 \mu m^2$. The angular divergence of about 4 mrad is larger than at conventional synchrotron sources and provides a circular field of view of about 6 cm at a distance of 16 m from the source, which can be utilized to measure relatively large biological samples. Detailed performance parameters of the CLS prototype, at which most of the experiments presented in this thesis were carried out, and of the planned MuCLS facility at the TUM Campus in Garching are given in table 2.1.

The X-ray spectrum emitted by the CLS is tunable via changes in the electron beam energy from 20 to 44 MeV, which results in an X-ray energy range from 10 to 35 keV. Fig. 2.7 shows a measured X-ray spectrum with a peak energy of 21 keV. The X-ray energy can thus be freely chosen and tuned to optimum contrast for the experimental question at hand. The high degree of spatial and temporal coherence can be exploited in the straightforward use of refraction-based imaging techniques as published in Bech...
Figure 2.6.: Top: Compact Light Source (CLS) CAD drawing. The inset shows a sketch of the interaction region of focused electron and photon bunch with matched waists. Below: A picture of the CLS prototype. Images courtesy of R. Ruth Lyncean Technologies.
2.4. Laser-driven X-ray sources

Figure 2.7.: CLS spectrum with a peak energy at 21 keV. The spectrum was recorded with an Amptek XR-100CR detector. The background signal above the peak is due to pile-up of the detector.

et al. (2009); Schleede et al. (2012a,b); Bech et al. (2012), and presented in chapter 6 to 8 of this thesis. The intrinsic energy bandwidth of $\Delta E/E_{\text{peak}} = 3\%$ allows for monochromatic biomedical imaging experiments avoiding beam hardening artifacts present in polychromatic measurements. An experimental demonstration is given in chapter 7 and has previously been published in Achterhold et al. (2013). The high monochromatic flux has further been used for protein crystallography measurements published in Abendroth et al. (2010).
<table>
<thead>
<tr>
<th>Machine</th>
<th>CLS prototype</th>
<th>MuCLS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electron beam</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>repetition rate</td>
<td>65 MHz (single bunch)</td>
<td>65 MHz (single bunch)</td>
</tr>
<tr>
<td>electron energy</td>
<td>20 to 44 MeV</td>
<td>20 to 44 MeV</td>
</tr>
<tr>
<td>bunch length</td>
<td>50 ps/1.5 cm (rms)</td>
<td>50 ps/1.5 cm (rms)</td>
</tr>
<tr>
<td>bunch charge</td>
<td>0.3 nC</td>
<td>0.6 nC</td>
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<tr>
<td>current</td>
<td>20 mA</td>
<td>40 mA</td>
</tr>
<tr>
<td>focus spot size</td>
<td>$60 \times 60 , \mu m^2$</td>
<td>$45 \times 45 , \mu m^2$</td>
</tr>
<tr>
<td><strong>Laser &amp; Resonator</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>repetition rate</td>
<td>65 MHz</td>
<td>65 MHz</td>
</tr>
<tr>
<td>wavelength</td>
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<td>1064 nm</td>
</tr>
<tr>
<td>pulse length (FWHM)</td>
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<td>30 ps</td>
</tr>
<tr>
<td>mean power</td>
<td>10 W</td>
<td>25 W</td>
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<tr>
<td>power in resonator</td>
<td>40 kW</td>
<td>100 kW</td>
</tr>
<tr>
<td>Finesse, efficiency</td>
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<td>15000 with 70%</td>
</tr>
<tr>
<td>pulse energy (resonator)</td>
<td>0.6 mJ</td>
<td>1.5 mJ</td>
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<td>peak power (resonator)</td>
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<td>$\sim50$ MW</td>
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<td>peak power density (focus)</td>
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<td>$\sim650$ GW/cm$^2$</td>
</tr>
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<td><strong>X-ray beam</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>energy range</td>
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<td>10 to 35 keV</td>
</tr>
<tr>
<td>intrinsic bandwidth</td>
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<td>3 to 5%</td>
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<tr>
<td>source size</td>
<td>$50 \times 50 , \mu m^2$ (rms)</td>
<td>$35 \times 35 , \mu m^2$ (rms)</td>
</tr>
<tr>
<td>Brilliance$^1$</td>
<td>$5 \times 10^9$</td>
<td>$1 \times 10^{11}$</td>
</tr>
<tr>
<td>Flux (in 4 mrad cone)</td>
<td>$2 \times 10^{10}$ photons s$^{-1}$</td>
<td>$1 \times 10^{11}$ photons s$^{-1}$</td>
</tr>
</tbody>
</table>

$^1$ given in photons s$^{-1}$ mm$^{-2}$ mrad$^{-2}$ per 0.1% bandwidth

Table 2.1.: Performance parameters of the CLS prototype and the planned MuCLS facility (Ruth, 2013).
2.4. Laser-driven X-ray sources

2.4.4. Laser-plasma sources

Due to limited field gradients, synchrotrons and FELs need large-scale radio-frequency electron accelerators to reach the electron energies necessary for hard X-ray generation. Laser wakefield acceleration (LWFA) (Esarey et al., 2009) is a compact alternative as it achieves relativistic electron energies up to GeV on cm scale interaction areas. This is due to the fact that laser induced ionized plasmas can sustain electric field gradients three orders of magnitude higher than accessible with conventional accelerator technology. Furthermore, fs electron bunches are produced, which are intrinsically synchronized with the driving laser, allowing for pump-and-probe experiments.

Electron acceleration

In LWFA, an ultra-intense (> $10^{18}$ W/cm$^2$), short (~fs) laser pulse is focused onto a gas cell, in which the gas becomes fully ionized. As the laser pulse propagates through the dilute (underdense) plasma, it moves the lighter electrons away from the heavier ions and thereby introduces a plasma wave, which trails the laser pulse and induces oscillations at an angular frequency $\omega_p$ (Willmott, 2011):

$$\omega_p = \sqrt{n_e e^2 / m_e \epsilon_0}.$$ (2.22)

Here, $n_e$, $e$, and $m_e$ are the density, charge and rest mass of the plasma electrons, and $\epsilon_0$ is the vacuum permittivity. This wave features longitudinal electric fields, which exceed conventional accelerator technology by three orders of magnitude. Electrons that are trapped or injected into these regions can be accelerated to GeV energy on a cm scale if the laser pulse is not refracted from the interaction region. The electron beam emittance is comparable to available conventional linear accelerators. The bunch length is a fraction of the plasma wavelength, which is on the order of $\sim 10 - 100 \mu$m, and corresponds to very short bunches on the order of 5 fs FWHM (Buck et al., 2011; Lundh et al., 2011). The processes of electron trapping, focusing in the plasma and electron injection is beyond the scope of this thesis and the reader is refereed to Esarey et al. (2009).

Repetition rates are limited by the repetition rate of the high power laser system, which is typically on the order of $\sim 10$ Hz and the shot to shot stability in LWFA is currently lower than what is achieved using conventional accelerator technology.

X-ray generation

Electron bunches accelerated in a laser plasma are well suited for a subsequent generation of X-rays. Different concepts have been realized:

- **Conventional undulator**: A combination of electron bunches, which are accelerated to 210 MeV within 1.5 cm, with a short, 30 cm-long undulator featuring periods of 5 mm was used for soft X-ray generation down to wavelengths of $\lambda = 7$ nm
with an X-ray pulse duration dominated by electron bunch length of 10 fs (Fuchs et al., 2009). To create hard X-rays either the electron energy would have to be increased or the undulator period further reduced (compare equation 2.10).

- **Inverse Compton scattering:** An undulator period with reduced period is realized using inverse Compton scattering of the accelerated electron bunch with a counter propagating laser pulse. This results in an all-optical source experimentally demonstrated by Ta Phuoc et al. (2012).

- **Betatron radiation in plasma:** Betatron radiation in plasma is an all-optical X-ray source, which is discussed in more detail below.

In certain plasma-wave regimes and under specific electron injection settings (details on the “bubble-regime” can be found in Esarey et al. (2009)), the electrons that are accelerated in a plasma also undergo transverse betatron oscillation in focusing fields of the plasma wave. During the acceleration process the electrons are wiggled transversely by the strong radial fields of the plasma wave, causing them to emit a forward-directed, incoherent X-ray beam, comparable to a wiggler spectrum and in the following referred to as betatron radiation. The plasma wavelength \( \lambda_p = \frac{2\pi c}{\omega_p} \) (Esarey et al., 2009) confines the wakefield to a radius on the order of \( \sim 10 \mu m \). The betatron oscillation frequency is defined by the plasma frequency \( \omega_p; \omega_\beta = \omega_p / \sqrt{2\gamma} \). Here, \( \gamma \) is the relativistic factor of the electron beam. The spectrum features a critical energy of \( E_{\text{crit}} = \frac{3h}{2\pi} K \gamma^2 \omega_\beta \) with the Planck constant \( h \) and the wiggler parameter \( K \) (Kneip et al., 2010), which is defined via the radiation opening angle \( \theta \): \( K = \gamma \theta \).

The benefits of these sources include short pulse lengths, a small source size (high spatial coherence) and a synchronization of the electron bunches and thus the emitted X-rays with the drive laser. Betatron radiation and the combination of laser wakefield acceleration with inverse Compton scattering constitute one of the first all-optical compact sources of hard X-rays available. Currently the main drawback of these sources is a low average brilliance, which is limited by the repetition rate of the high power lasers used.

The potential of laser-driven betatron sources for recording single-shot X-ray phase-contrast images based on the free-space propagation technique was demonstrated in Fourmaux et al. (2011). In chapter 9 the first phase-contrast CT obtained at the betatron facility at the MPI for Quantum Optics is presented.
Chapter 3. Principles of X-ray imaging

3. Principles of X-ray imaging

The interaction of X-rays with matter is the key to an understanding of different material contrasts used in X-ray imaging today. Unlike conventional X-ray imaging, which relies on contrast generation through the different absorption properties of materials, phase-contrast imaging techniques employ the refraction of X-rays. The main focus of this chapter lies on the theory of how X-rays are absorbed and refracted, how an X-ray wavefront propagates, as well as how a measurement of the X-ray wave’s phase is realized among different phase-contrast imaging techniques.

The chapter is structured as follows: X-ray absorption and refraction is discussed in the context of a plane wave propagating in a medium represented by its complex refractive index in section 3.1.1 and 3.1.2. Subsequently, the complex refractive index is related to microscopic properties of the material, namely electron distributions and binding energies in section 3.1.3. In section 3.2 we give an overview over existing phase-contrast imaging techniques. The propagation of a modulated wavefront from a sample or optic exit plane to the detector is discussed in section 3.3. Data acquisition and data processing is discussed in detail for the imaging techniques that were used to record results presented in this thesis: propagation-based imaging and grating-based interferometry, which are discussed in section 3.4 and section 3.5 respectively. The chapter concludes with a brief introduction of the main formalisms of CT in section 3.6.

3.1. X-ray interactions with matter

X-ray energies are typically in the range of or larger than binding energies of inner shell electrons. Thus, X-rays mainly interact with these electrons when interacting with a material. For the X-ray energy ranges concerned in this thesis, namely 1 keV to 36 keV, the contribution from higher energy processes like pair production are negligible (Willmott, 2011). Therefore, the possible interaction mechanism comprise: Elastic scattering, inelastic scattering and photoelectric absorption. Inelastic scattering or Compton scattering is described in a relativistic particle picture of X-rays, in which a photon that is scattered at an electron loses part of its energy, which constitutes an inelastic scattering process. Elastic scattering of X-rays at free electrons (Thomson scattering) or bound electrons (Rayleigh scattering) can be described in a semiclassical picture, in which an electron is forced to oscillate in the field of an incoming electromagnetic wave. The electron thereby reemits X-rays of the same wavelength. In the process of photoelectric absorption, an X-ray photon is absorbed by the atom. Photoelectric absorption and Compton scattering are the main contributions to conventional attenuation-based image contrast formation, where the latter gains influence only at high X-ray energies and high atomic numbers. Elastic scattering is the basis for the formation of phase-contrast
3.1. X-ray interactions with matter

![Diagram of X-ray interaction with matter](image)

**Figure 3.1.** A plane wave that interacts with a material of complex refractive index \( n \) experiences a phase shift \( \Delta \Phi \) and an amplitude decay \( \Delta A \) compared to an unperturbed wave in vacuum. The phase shift corresponds to a change in the direction of propagation—refraction—by a small angle \( \alpha \).

To describe absorption and refraction effects, we will use the macroscopic, phenomenological concept of a complex refractive index, which is well known from the description of visible light interaction with matter. The higher energy of X-rays accounts for significantly different optical properties, namely an index of refraction in which the real part is by a small decrement \( \delta \) less than one and sharp absorption edges corresponding to inner shell electron binding energies.

### 3.1.1. Complex refractive index

X-rays that propagate through a medium of complex refractive index \( n \) experience a phase shift \( \Delta \Phi \), due to an increased phase velocity in the medium, as well as attenuation, i.e. a decrease in amplitude \( \Delta A \), as sketched in Fig. 3.1. The complex refractive index is defined by:

\[
n = 1 - \delta + i\beta.
\]  

(3.1)

Here the real part \( 1 - \delta \) accounts for elastic interaction and the imaginary part \( \beta \) for inelastic processes. For silicon at 21 keV, values of \( \delta = 1.09 \cdot 10^{-06} \) and \( \beta = 3.92 \cdot 10^{-09} \) are tabulated\(^1\). Via Snell’s law one can estimate the refraction angle caused by a Si wedge that is inclined at an angle of 89° with respect to the direction of propagation. The resulting refraction angle, \( \alpha = -1.9 \cdot 10^{-08} \) rad is very small and illustrates the challenge of measuring phase shifts in the X-ray regime. Please note that both \( \delta \) and \( \beta \) show a distinct dependency on energy as will be discussed in section 3.1.3. In the following we will relate the refractive index \( n \) to the phase shift and the amplitude decrease of an idealized plane monochromatic X-ray wave.

\(^1\)http://henke.lbl.gov/optical_constants/getdb2.html
3.1.2. X-ray attenuation and phase shift

We assume an idealized plane linearly polarized X-ray wave of wavevector $k_0 = 2\pi/\lambda$, wavelength $\lambda$, angular frequency $\omega$, amplitude $E_0$, propagating in z-direction in vacuum and in a homogeneous material of complex refractive index $n$:

\[
\begin{align*}
\text{vacuum: } E(z,t)_v &= E_0 \cdot \exp\left[i \left( k_0 z - \omega t \right) \right], \\
\text{medium: } E(z,t)_m &= E_0 \cdot \exp\left[i \left( nk_0 z - \omega t \right) \right] \cdot \exp\left[-k_0 \beta z \right] \cdot \exp\left[i k_0 \delta z \right].
\end{align*}
\]

where subscripts $v$ and $m$ denote vacuum and material respectively. The resulting term $E(z,t)_m$ is divided into the unperturbed wave, a factor that accounts for an amplitude decay and one that introduces a phase shift.

**X-ray attenuation in material:** An amplitude decay by $\exp[-k_0 \beta z]$ corresponds to an intensity decay of:

\[
\frac{I(z)}{I_0} = \frac{|E(z,t)_m|^2}{|E(z,t)_v|^2} = e^{-2k_0 \beta z}.
\]

A comparison with the well known Beer-Lambert law for the absorption of X-rays,

\[
\frac{I(z)}{I_0} = e^{-\mu z},
\]

yields a relation between imaginary part of the refractive index $\beta$ and the linear attenuation coefficient $\mu = 2k_0 \beta$.

**X-ray Phase shift in material:** The phase shift $\Delta \Phi$ of the wave that passed through the material as opposed to the unperturbed wave in vacuum is:

\[
\Delta \Phi = k_0 \delta z.
\]

The phase of a wavefront wavefront $\Phi(x)$ that propagated through a phase shifting object extended along $x$ (perpendicular to the direction of propagation), can be related to a refraction angle $\alpha$. A line through wave crests in Fig. 3.1 indicates this effect. Using a small angle approximation yields:

\[
\alpha(x) = \frac{\lambda}{2\pi} \frac{\partial \Phi}{\partial x}
\]

The measurement of X-ray deflection angles thus yields the first derivative of the phase shift of the X-ray wavefront.

If multiple materials of differing refractive index are traversed, equation 3.6 and 3.7 have to be extended to the integral of $\delta$ and $\beta$ along the X-ray path in direction $z$:

\[
\ln \left( \frac{I}{I_0} \right) = - \int_0^z \mu(z) dz
\]

\[
\Delta \Phi = \int_0^z k_0 \delta(z) dz.
\]
Here we made use of the projection approximation, i.e. we assumed that X-rays travel on a straight path through a medium. The interaction between X-rays and matter is rather weak such that multiple scattering events are unlikely and the phase and absorption interaction in a 3D object can be described by the interaction in a single plane (Paganin, 2006).

### 3.1.3. Material dependency

Real and imaginary part of the complex refractive index are defined via microscopic interactions of X-rays with electrons in a material. In a semiclassical picture electrons are bound to atoms and forced to oscillate in an external field. They thereby reemit a spherical wave $e^{i k R} / R$ of the same energy (Als-Nielsen and McMorrow, 2011):

$$\frac{|E_{\text{out}}|}{|E_{\text{in}}|} = -r_e \cdot f(q, E) \cdot P \cdot e^{i k R} / R.$$  (3.11)

The outgoing field amplitude $E_{\text{out}}$ (wavevektor $\vec{k}'$) is related to the incoming field amplitude $E_{\text{in}}$ (wavevektor $\vec{k}$) through the classical electron radius $r_e$ and the atomic form factor $f(q, E)$ (also called atomic scattering factor), which denotes the ratio between electric field amplitude scattered by multiple bound electrons in a material relative to the electric field amplitude from scattering at a single free electron. The scattering vector $q$ is defined via $\vec{q} = \vec{k}' - \vec{k}$. The atomic form factor thus accounts for the fact that in a material X-rays interact with a larger number of electrons distributed in space and bound to atoms; $P$ accounts for the polarization of the wave.

Scattering from multiple free (unbound) electrons is described by a form factor, which is given by the Fourier transform of the charge distribution (Als-Nielsen and McMorrow, 2011). If only forward scattering is concerned the term becomes independent of the position of electrons and the real part simplifies to $f_0(\theta = 0) \approx Z$ (Attwood, 2007). For X-rays that are sufficiently far away from absorption edges the assumption of a free electron is justified and the form factor in forward direction is independent of X-ray energy.

The interaction of X-rays with bound electrons can be described using the analogy of electrons being externally driven, damped harmonic oscillators. Thereby energy dependent real and imaginary dispersion corrections to the atomic form factor—$f_1(E)$ and $f_2(E)$—are introduced, whose influence increases when the driving X-ray frequency $\omega$ approaches a resonance frequency $\omega_r$. The atomic form factor is then given by the sum of the former (Als-Nielsen and McMorrow, 2011):

$$f(q, E) = f_0(q) + f_1(E) + i f_2(E)$$  (3.12)

The detailed derivation and discussion of the above terms is beyond the scope of this thesis and the reader is referred to Attwood (2007). At this point we would like to note that dispersion corrections are needed to describe the behavior of the form factor in the vicinity of resonances, i.e. close to absorption edges. The dispersion corrections to the form factor are exploited in crystallography techniques, e.g. Multi-wavelength Anomalous Diffraction (MAD), where diffraction patterns at multiple energies around an absorption edge are recoded in order to solve the complex structure of macromolecules.
Chapter 3. Principles of X-ray imaging

such as proteins (Als-Nielsen and McMorrow, 2011).

In the following we will only consider scattering in the forward direction, which is related to the complex refractive index via (Willmott, 2011):

$$n = 1 - \frac{r_e}{2\pi} \lambda^2 \sum_i N_i f^i (\theta = 0),$$  \hspace{1cm} (3.13)

with $N_i$ being the number of atoms per unit volume and $f^i (\theta = 0)$, the complex atomic form factor of the $i$th atom. Furthermore, we assume to be sufficiently far from absorption edges to neglect the dispersion correction $f_1$. The real part of the form factor is thus given by $f_0 (\theta = 0) \approx Z$. Equation 3.13 yields:

$$\delta = \frac{r_e}{2\pi} \lambda^2 \rho_e,$$  \hspace{1cm} (3.14)

with the electron density $\rho_e = N_i \cdot Z$. The refractive index decrement exhibits a $1/E^2$-dependence on X-ray energy and a linear dependence on $Z$. Phase-contrast imaging thus probes electron density differences in the sample.

The linear attenuation coefficient $\mu$ is defined via the total atomic absorption cross section $\sigma_a$ and the atomic number density $\rho_a$ (Als-Nielsen and McMorrow, 2011):

$$\mu = 2k_0\beta = \rho_a \sigma_a.$$  \hspace{1cm} (3.15)

The atomic number density is given by: $\rho_a = (\rho_M N_A)/M$, with a mass density $\rho_M$, Avogadro's number $N_A$ and molar mass $M$. The approximated dependency of $\sigma_a \propto Z^4$ on atomic number $Z$ accounts for image contrast between materials with differing $Z$ and the penetration power of high-energy X-rays is related to a decrease of $\sigma_a$ with energy by $1/E^3$, when moving away from absorption edges (Willmott, 2011). Equation 3.13 and 3.15 can be used to relate $\sigma_a$ to $f_2 (E)$.

Above all absorption edges $\delta$ falls of less quickly ($\propto E^{-2}$) with increasing energy than $\beta$ ($\propto E^{-4}$), which offers the potential for increased image contrast at higher energies and therefore lower dose applied to the patient.

3.2. Phase-sensitive X-ray imaging methods

In this section, we will discuss different methods that are used to measure the phase of an X-ray wave after propagating through a sample. All techniques aim at transferring the small phase shifts imprinted on the X-ray wavefront to measurable intensity changes. The methods described in the following differ significantly in terms of beam coherence requirements, and thus in prospects for the use with lab sources and clinical implementation. Furthermore, techniques can be differentiated by the provided phase signal, which is the phase shift, $\Phi$, in the case of the crystal interferometer (CI), the first derivative, $\partial \Phi / \partial x$, in the case of crystal analyzer (ABI) and grating-based techniques (GBI) and the second derivative in the case of propagation-based phase-contrast imaging (PBI).
Crystal interferometry
In the 1960s, crystal interferometry was the first phase-contrast imaging technique to be realized in the hard X-ray regime (Bonse and Hart, 1965). A schematic of a crystal interferometer is sketched in Fig. 3.2 (a). The first crystal divides the beam into diffracted and forward diffracted components, the second bar redirects the two beams, where one beam passes through a sample and the second one serves as a reference. At the third crystal the beams overlap and produce an interference pattern from which the phase $\Phi$ imprinted on the wavefront can be deduced. It is known to be the most sensitive of the available phase-contrast techniques (Momose, 2005).

The crystals have to be aligned with a precision on the order of the X-ray wavelength, which makes crystal interferometers extremely sensitive to vibrations. If a single crystal with monolithically cut bars is used, this difficulty is circumvented at the expense of a limited field of view (Momose, 2003). Moreover, the technique makes use of the Bragg condition and therefore relies on a monochromatic, highly collimated beam, which is only provided by synchrotron sources.

Crystal analyzer-based imaging
In diffraction-enhanced imaging (DEI) or analyzer-based imaging (ABI) a crystal analyzer is mounted between the object and the detector (compare schematic in Fig. 3.2 (b)) (Davis et al., 1995; Chapman et al., 1997). Reflection from the analyzer crystal only occurs for X-rays in a small angular range meeting the Bragg condition of the crystal. Tilting the crystal while monitoring the intensity in each pixel generates a rocking curve, from which absorption, differential phase and small-angle scattering information of the sample can be extracted (Khelashvili et al., 2006; Rigon et al., 2007). The provided signals—comparable to the signals obtained by GBI—are obtained from this rocking curve: attenuation is calculated from the integrated intensity, the shift of curve’s centroid yields the refraction angle and broadening of the curve is associated with ultra-small angle scattering (USAXS) on structure sizes below the resolution of the imaging system but significantly larger than the X-ray wavelength used. As in GBI the angular deviation of the beam is measured, which is proportional to the first derivative of the phase front along one dimension.

In simplified acquisition schemes, not the entire rocking curve but rather only a single image is recoded. One example is the peak of the rocking curve, where images exhibit strong extinction contrast as nearly no scattered photons reach the detector. Alternatively images taken on the slope of the rocking curve produce phase-enhanced images. In these images, the relation of the signal to the actual phase shift is not trivial, as scattering and attenuation contributions to the curve are not clearly separated.

Due to the narrow bandwidth selected by the Bragg condition of the crystal, high monochromatic flux, and a highly collimated beam is required. Thus, ABI is typically performed at large-scale synchrotron X-ray sources. The use of DEI with lab sources suffers from low monochromatic flux and the resulting long exposure times, which are not compatible with in-vivo imaging applications (Parham et al., 2009; Nesch et al., 2009). The use of ABI in the context of small animal lung imaging is discussed in section 6.2.
Figure 3.2.: Schematics of different phase-contrast imaging techniques. Please note that in (a) diffracted beams that do not contribute to image formation have been omitted.
3.2. Phase-sensitive X-ray imaging methods

Propagation-based imaging
In propagation-based imaging (PBI), the sample is illuminated by a spatially coherent source, which creates a Fresnel diffraction pattern after a certain propagation distance behind the sample (compare sketch in Fig. 3.2 (c)). These interference effects result in the formation of intensity modulations, i.e. fringes, at object interfaces, which produces a so called edge-enhanced image (Snigirev et al., 1995). PBI is often referred to as inline holography (Cloetens et al., 1999). In general, the Laplacian of the phase front is encoded in the image intensity modulations. To retrieve the phase, images at different propagation distances are taken. If, however, certain restrictions on the sample such as low absorption or a single material constraint are justified, the phase can be retrieved from a single propagation distance (Paganin et al., 2002).

In addition to a high degree of spatial coherence, which is either provided by a micro-focus source or realized by a large source to sample distance, a high resolution detector is needed to resolve refraction-induced interference fringes. Advantages of the technique comprise the fact that no optical elements have to be used and thus the field of view is only limited by the beam size at the sample position and the size of the detector. Furthermore the technique has proven to work with polychromatic illumination (Wilkins et al., 1996). Unlike GBI and ABI, which generally feature unidirectional sensitivity, PBI is sensitive to phase changes in all directions. More details on data acquisition and processing are given in section 3.4 and experimental results of a propagation-based CT measurement from a betatron laser-plasma source are presented in chapter 9. PBI is discussed in the context of lung imaging and mammography in section 6.2 and 8.1 respectively.

Grating interferometry
In grating-based imaging (GBI), a first grating acts as a beam splitter and separates the X-ray beam into diffraction orders, which overlap and interfere provided that the illuminating wavefront is spatially coherent. The intensity pattern that is thereby created is called Talbot carpet. Refraction from a sample causes a transverse shift of the intensity pattern, which is usually not directly resolvable and thus an absorbing grating with matching period—the analyzer grating—is used to translate small shifts of the intensity pattern into measurable changes of intensity in a much larger detector pixel. The phase signal extracted from a stepping curve is proportional to the first derivative of the phase front. The first projection images (Momose et al., 2003) and the first CT measurements (Momose, 2005; Weitkamp et al., 2005) were based on a two-grating interferometer setup and performed at synchrotron sources.

Comparable to ABI, GBI yields phase and dark-field images that are simultaneously obtained with the conventional attenuation-based X-ray image and thus provides three complementary image modalities that are intrinsically registered. Unlike DEI the grating-based interferometer supplies a large field of view and has also been shown to work with polychromatic sources and in cone-beam geometry (Weitkamp et al., 2005; Pfeiffer et al., 2007a, 2008). The technique can be used with extended sources in the combination with a source grating that creates a set of line sources fulfilling the requirements for spatial coherence (Pfeiffer et al., 2006). The vast majority of the results presented in this thesis were obtained with a two-grating interferometer and details on data acquisition and processing are given in section 3.5.
3.3. X-ray propagation

This section aims at presenting the basic concept used to propagate a given X-ray wavefront, e.g., after the interaction with a sample or X-ray optics, over a certain distance, e.g., to the detector. In X-ray imaging, one usually distinguishes three regimes, which are differentiated by how far a distance $D$ the X-ray wavefront is allowed to propagate after the sample, and by the structural size $a$ one wishes to image. In clinical imaging, we are usually in the contact mode, meaning that the detector is as close as possible to the patient to avoid penumbral blurring. The contact mode is insensitive to refraction effects due to the small value of refraction angles and the blurring associated with extended conventional sources. If the wavefield is allowed to propagate after the sample, interference between refracted and non-refracted waves modulate the intensity pattern. In the far-field limit (Fraunhofer diffraction) we can assume that waves originating from two points in the sample may be described by plane waves at the detector. As the error $\Delta$ to the optical path length difference described with spherical waves approaches $\lambda/2$, the far field goes over to the near field (Fresnel regime), in which propagation has to be described with spherical waves. The regimes are differentiated by:

\begin{align*}
\text{contact regime: } & D \ll \frac{a^2}{\lambda} \\
\text{near field: } & D \approx \frac{a^2}{\lambda} \\
\text{far-field: } & D \gg \frac{a^2}{\lambda}
\end{align*}

Thus, imaging of atomic structures $a \approx 1\text{Å}$ with $\lambda = 1\text{Å}$ is only feasible in the far-field regime (Als-Nielsen and McMorrow, 2011).

Imaging experiments presented in this thesis are performed in the near-field regime. Using Huygens principle, we can assume that the wavefront at any point can be calculated from summing over the contributions of point sources, which resemble the wavefront at an earlier point. In the near-field regime the Fresnel-diffraction integral can be used to calculate a wavefront at a detector plane $E(x,y,z)$ from a parallel sample exit plane $E(x',y',0)$ positioned at a distance $z = D$ (Goodman, 1996):

\begin{equation}
E(x,y,z) = \frac{e^{ikz}}{i\lambda z} \int \int E(x',y',0) \exp \left\{ \frac{ik}{2z} \left[ (x-x')^2 + (y-y')^2 \right] \right\} \, dx' \, dy'
\end{equation}

Please note that this corresponds to the convolution of the sample exit wave with a propagation term often called Fresnel propagator. Making use of the convolution theorem one can thus propagate a wavefront by multiplying the sample exit wave and the Fresnel propagator in Fourier space. This relation is for example used in the calculation of Talbot carpets from transmission or phase gratings. Derivations that precede the above formula, approximations used and the extension to the Fraunhofer regime is beyond the scope of this thesis and the reader is referred to a detailed discussion of the topic in Goodman (1996).
3.4. Propagation-based imaging

Propagation-based (or in-line) phase-contrast imaging (PBI) does not employ optical elements between the sample and the detector. Illumination with a spatially coherent source causes differently scattered waves from different parts of the sample to interfere after sufficient propagation of the wavefront. In the near-field regime Fresnel diffraction patterns (fringes) are formed due to the interference of the overlapping beams. Furthermore, the technique relies on high resolution detectors to resolve these interference fringes. The requirement on temporal coherence is less stringent, which is why the use of polychromatic microfocus sources has successfully been demonstrated.

The section is structured as follows: First, we will discuss the formation of qualitative phase images, namely the edge-enhanced image in section 3.4.1. The transport-of-intensity equation, which is the basis for a quantitative assessment of a sample’s refractive index is described in section 3.4.2. In order to retrieve the phase front, we make use of a single material constraint based on an algorithm by Paganin et al. (2002) and provide references to other commonly used phase retrieval methods in section 3.4.3. Coherence requirements of the technique are briefly discussed in section 3.4.4.

3.4.1. Edge enhancement

Images of a sample, which is illuminated by a spatially coherent wave, exhibit diffraction features at material boundaries if the wave is allowed to propagate after interaction with the material. These diffraction effects increase with increasing propagation distance, i.e. increasing overlap between differently diffracted beams. In the near-field regime edge-enhanced images are formed that resemble the object itself with enhanced material boundaries. The periodicity of interference fringes formed at an edge can be deduced from the numerical solution of the Fresnel diffraction integral (equation 3.19). A rough estimate on fringe spacing can however be obtained from a simplified geometrical approach (Willmott, 2011), where the distance of the first dark fringe (intensity minimum) from the edge $x_1$ is given by:

$$x_1 = \sqrt{\frac{D\lambda}{2}}.$$  \hspace{1cm} (3.20)

From this equation it is obvious that fringe spacing increases with increasing propagation distance $D$. Furthermore, the dependence on $\lambda$ causes a decrease in fringe contrast if contributions from polychromatic illuminations are considered. Mathematically the edge-enhanced image can be approximated by the Laplacian of the wavefront phase profile $\nabla^2_{xy} \Phi (x,y)$ if the smallest resolvable features are larger than the size of the first Fresnel zone $r > \sqrt{D\lambda}$ (Wilkins et al., 1996), i.e. if the size of the region contributing to the interference effect is small compared to the resolution of the system such that every sample border is enhanced from a separate fringe pattern. If the structure sizes are comparable to the radius of the first Fresnel zone, we enter the holographic regime. Edge-enhanced images can in general not be used for a subsequent quantitative CT reconstruction as they are not directly related to the projection of the refractive index decrement $\delta$, which we wish to assess. In order to obtain quantitative phase projection
images, a phase-retrieval step has to be performed, which is described in the following sections.

### 3.4.2. Transport-of-intensity equation

As introduced in the previous section, a wavefront can be described as a set of point sources yielding the Fresnel diffraction integral, which serves to calculate the forward problem, namely the propagation of the sample exit wavefront to the detector. The inverse problem, which consists of retrieving the (complex-valued) sample exit wavefront from measured intensities in the detector plane, is more challenging. One approach is to use the contrast transfer function formalism (also known as holo-tomography when combined with CT (Cloetens et al., 1999)). Another approach is to solve the so-called Transport-of-Intensity equation (TIE). The TIE is given by the paraxial approximation of the Helmholtz equation for a plane wave propagating along $z$ and describes the evolution of intensity of a monochromatic electromagnetic wave (Paganin, 2006):

\[
\nabla_\perp \cdot (I(\vec{r}_\perp, z) \nabla_\perp \Phi(\vec{r}_\perp, z)) = \frac{2\pi}{\lambda} \frac{\partial}{\partial z} I(\vec{r}_\perp, z).
\]

(3.21)

It relates the propagation of intensity distribution, i.e. the derivative along the direction of propagation $z$, to the phase distribution in planes perpendicular to the direction of propagation. The derivative with respect to $z$ is often approximated by finite differences. There are different approaches to solve the TIE in order to retrieve the projected phase at the sample exit plane $\Phi(z = 0)$ from edge-enhanced images at a certain propagation distance $D$. The attempts differ by amount of raw input needed and comprise iterative algorithms (Guigay et al., 2007) as well as the use of constraints on the sample to reduce required raw data (Burvall et al., 2011). The discussion of these approaches is beyond the scope of this thesis and the reader is referred to the references given above and in Paganin (2006).

The experimental results shown in this thesis were obtained by using a single material approximation as introduced in Paganin et al. (2002). This approach is shortly discussed in the following section.

### 3.4.3. Phase retrieval

In order to obtain quantitative phase projections from edge-enhanced images, a phase retrieval step is necessary. If this step is omitted, a CT reconstruction will be proportional to the Laplacian of the phase front and thus highlight material boundaries. The reconstructed gray value is not directly related to material properties and does thus not allow for volume data analysis such as automated segmentation. The reconstruction from phase-retrieved projections exhibits area contrast as known from absorption imaging and thus allows for a quantitative analysis of CT volume data as well as the use of standard segmentation and visualization tools.

One approach for phase retrieval of images taken at a single defocusing distance is given by Paganin et al. (2002). The algorithm assumes that: (1) the sample can be approximated to be composed of a single material with a constant value of $\delta/\beta$, i.e. homogeneous elemental composition but varying density; (2) monochromatic illumination;
3.4. Propagation-based imaging

(3) images are taken in the near field (i.e. equation 3.17 holds). The approach follows from the TIE (equation 3.21) by describing phase and intensity directly after the sample \( z = 0 \) (contact image) in terms of the projected thickness and by using contact image and propagated image in a finite difference approximation for the derivative with respect to \( z \). This approach yields the projected thickness \( T(\vec{r}) \) of the sample, which is directly related to the phase shift imposed onto the wavefront via \( \Phi(\vec{r}) = -2\pi/\lambda \delta T(\vec{r}) \) (Paganin et al., 2002):

\[
T(\vec{r}) = -\frac{1}{\mu} \ln \left( \mathcal{F}^{-1} \left\{ \mathcal{F} \left\{ \frac{I(\vec{r}, z = D)}{I_0} \right\} \right\} \right),
\]

(3.22)

where \( \vec{r} \) are the transverse coordinates, \( \vec{k} \) are the Fourier space coordinates, \( I \) is the measured intensity, \( I_0 \) is the uniform intensity of the incident radiation, \( D \) is the distance from the sample to the detector and \( \delta \) and \( \mu \) are the material dependent linear absorption coefficient and refractive index decrement, respectively.

Please note that in the above formulas we have assumed a parallel beam geometry. The diffraction image under point source illumination (cone beam geometry) is related to the parallel beam diffraction image by the Fresnel scaling theorem. The cone beam measurement is equivalent to a parallel beam measurement at an effective propagation distance \( D_{\text{eff}} = D/M \), magnified by \( M = (D + l)/l \) and its intensity divided by \( M^2 \) (Paganin et al., 2002; Paganin, 2006), where \( l \) is the distance from source to sample. This scaling is used in the phase retrieval from cone-beam experimental data in section 9.5.

3.4.4. Coherence

Limited spatial coherence

The main requirement for PBI is that the transverse coherence length, given by \( l_t = \lambda/2 \cdot l/\sigma \) is larger than \( \sqrt{\lambda D/(2\sqrt{2})} \) (Cloetens et al., 1997). This corresponds to a coherence requirement over the Fresnel zone, i.e. over those points around the object that contribute to the image of this feature (Cloetens, 1999). Here, \( \lambda \) is the wavelength, \( D \) is the defocusing distance, \( \sigma \) is the source size. Convolution of the projected angular source size \( \sigma/l \) with the Fresnel pattern obtained from a single point source can be used to model the blurring of the interference fringes introduced by extended sources.

The above criterion is met by third-generation synchrotrons, but their size and cost prevent their proliferation in hospitals and small research institutions. Microfocus X-ray tubes provide the desired spatial coherence but suffer from a modest X-ray flux, implying lengthy exposure times. Laser-based betatron sources might become a compact high brilliance alternative, where first benchmark CT results are presented in this thesis in chapter 9.

Limited longitudinal coherence

PBI does not require substantial temporal coherence of the source and has proven to yield substantial contrast with polychromatic microfocus tube sources (Wilkins et al., 1996). The use of the above described phase retrieval approach with polychromatic sources has been demonstrated (Mayo et al., 2003; Arhatari et al., 2008). A detailed discussion on the effects of limited coherence can be found in (Wilkins et al., 1996).
Grating-based phase-contrast imaging has the advantage of being compatible with extended sources, i.e. low spatial coherence, and is discussed in the following sections.

3.5. Grating interferometry

Phase-contrast imaging relies on the transformation of small refraction angles into measurable changes of intensity. In grating interferometry changes in an intensity reference pattern—the Talbot carpet—are used to detect the following effects: attenuation, refraction, and scattering in the sample. These are encoded in a decrease in intensity, lateral shifts and a local decrease in coherence of the intensity pattern.

In this section the creation of the reference pattern via the Talbot effect is introduced. Subsequently, we will describe how data is recorded with the help of an analyzer grating. The section concludes with the description of how attenuation, phase, and scattering images are calculated from measured values.

3.5.1. Talbot effect

The Talbot effect was first discovered with visible light and describes the self imaging phenomenon of periodic structures under coherent illumination (Talbot, 1836). This means that a periodic wavefront, e.g. an intensity modulation from an absorbing grating with alternating spaces and absorbing bars, is reproduced after certain propagation distances, called Talbot distances. A pattern of periodicity \( p_1 \) is reproduced at full Talbot distances \( d_T \):

\[
d_T = \frac{2p_1^2}{\lambda}.
\]

Absorbing structures remove half of the intensity provided by the source from the imaging experiment. To circumvent this decrease in available flux, phase shifting gratings are usually used. The height of the grating bars is then determined by the desired phase shift (most often \( \Delta \Phi = \pi \) or \( \Delta \Phi = \pi/2 \)) and thus dependent on the X-ray energy and the grating material used (compare equation 3.10). Maximum intensity modulations can be found at fractional Talbot distances (Weitkamp et al., 2006):

\[
d_n = \frac{n}{2\lambda}p_1^2 \quad (n = 0, 1, 2, \ldots),
\]

with a periodicity of the interference pattern \( p_1 = p_1 \), produced by a \( \pi/2 \)-shift grating, and with a periodicity of \( p_1 = p_1/2 \) in the case of a \( \pi \)-shifting grating. Phase gratings produce maximum intensity modulations at odd Talbot orders, namely \( n = 1, 3, 5, \ldots \). Using this notation \( n = 5 \) corresponds to the fifth fractional Talbot distance.

We have limited this discussion to one-dimensional grating structures. Two-dimensional gratings are sensitive to the phase gradient in two directions (Zanette et al., 2010) and are discussed in the context of phase retrieval methods in section 5.5. Furthermore, we assumed a duty cycle of 0.5, i.e. equal width of grating bars and spaces.

Please note that the periodicity of the intensity pattern has to be on the order of the lateral shifts—refraction angles—that one wishes to detect. As these refraction angles
are very small, compact setups corresponding to short Talbot distances $d$, thus need µm-periodicity structures. At the same time grating bars have to be high enough to fully absorb (analyzer grating) or sufficiently shift (phase grating) hard X-rays, resulting in structure heights in the order of 50-100 µm. Such high aspect ratios are obtained with state of the art microfabrication techniques including photolithography, anisotropic wet etching, deep silicon etching, electroplating and LIGA (David et al., 2007; Mohr et al., 2012).

### 3.5.2. Grating interferometer

**Working principle**

The purpose of using a grating interferometer is to measure refraction and scattering in the sample in addition to the attenuation signal. Refraction and coherence degradation is assessed through the measurement of lateral shifts and contrast decrease of an intensity reference pattern, which is produced by the Talbot effect.

A sketch of the working principle of a grating interferometer is presented in Fig. 3.3. A photograph of an actual experimental setup can be found in Fig. 4.2. In the following, we will discuss the process of image formation starting at the sample position and then moving along the beam propagation direction $z$. An incoming wavefront is locally distorted by idealized samples. The green sample only absorbs X-rays, the red sample only introduces a phase shift, i.e. a small refraction angle, and in the blue sample microstructures with sizes below the resolution of the imaging system scatter the beam.

The phase grating, which comprises alternating phase shifting bars and spaces creates an intensity pattern called self-image with periodicity $p_I$ at fractional Talbot distances along the beam propagation direction $z$. If a sample is inserted in the beam path the X-ray wavefront is locally distorted and the intensity pattern is changed accordingly: its amplitude is decreased (green), it is shifted along direction $x$ (red), its contrast is decreased (blue)). These changes are not directly resolved by the much larger detector pixels (not sketched to scale in Fig. 4.2). Thus, an analyzer grating is inserted at a fractional Talbot distance. The analyzer grating consists of alternating highly absorbing bars and spaces with a periodicity that matches the interference pattern $p_2 = p_I$. In order to determine the shape and relative position of the modified interference pattern, the analyzer grating is moved along the $x$-direction performing a so called phase-stepping scan (compare curves in Fig. 3.3). The calculation of attenuation, differential-phase and dark-field images from these phase stepping series is described in section 3.5.3

**Magnifying geometry**

If the source deviates from a plane wave, the geometric magnification of the setup $M = (L + d) / d$ has to be taken into account. Here $L$ denotes the distance from the source to the first grating and $d$ describes inter-grating distance. As the intensity pattern created by the first grating is magnified to $p'_I = Mp_I$, the periodicity of the analyzer grating has to be increased accordingly. The Talbot distances are scaled to $d' = Md$.

**Moiré fringes**

Please note that both, a mismatch in interference pattern period $p_I$ and analyzer grating period $p_2$, as well as small tilt angles between the grating structures, result in the
Figure 3.3.: Working principle of the grating interferometer. An incoming wavefront is locally distorted by three different idealized samples, i.e. attenuating, phase shifting and scattering. The phase grating produces an intensity pattern. This pattern is locally shifted at sample positions where the wavefront is distorted. This shift is not directly resolved by the much larger (not sketched to scale) detector pixels. Thus, an analyzer grating is added to the setup and moved along \( x \) and at several positions \( x_g \) an image is recorded. This translates the angular shift into measurable intensity changes. The signatures of the idealized samples in the intensity pattern and the resulting changes in the recorded phase-stepping curves are indicated. In the stepping curves, the effect of an extended illuminating source is taken into account, which results in a sinusoidally shaped stepping curve instead of a triangular shape in the case of idealized plane wave illumination.
generation of the so called Moiré fringes (Weitkamp et al., 2004). If tilt angle and period mismatch are sufficiently small, these Moiré fringes constitute intensity modulations that are directly resolvable by the detector and can be used for source and optics metrology. An introduction to the topic can be found in Rutishauser (2013).

One alternative to the phase-stepping approach is single-shot Moiré-fringe imaging. Changes in the resolvable Moiré carrier fringe pattern are analyzed using a 2D Fourier transform of the image. Compared to the phase-stepping approach, signal sensitivity remains unaltered, whereas the resolution is decreased to the periodicity of the introduced carrier fringes. Thus, image resolution is traded for faster image acquisition (Takeda et al., 1982; Momose et al., 2009).

**Refraction angle and differential phase signal**

The phase shift induced by the red sample in Fig. 3.3 is related to a small refraction angle \( \alpha \) via equation 3.8. The intensity pattern is shifted along \( x \) by:

\[
 s_x = \alpha \cdot d, \tag{3.25}
\]

where \( s_x \) increases with increasing inter-grating distance \( d \) (again using a small angle approximation).

Differential phase measurements thus rely on the exact determination of the position of the interference pattern in relation to the pattern that has not been shifted. This position determination is accomplished in a stepping scan, which is described in the following.

### 3.5.3. Phase stepping and Fourier processing

Different positions of the analyzer grating \( x_g \) (along \( x \) in Fig. 3.3) correspond to alternating high and low intensity measured in a detector pixel behind the grating, depending on whether or not an interference pattern maximum is blocked by an absorbing bar. The intensity oscillation in each pixel, which is recorded at different transverse positions \( x_g \), is called stepping curve (compare curves on the right in Fig. 3.3). To account for non perfect illumination over the field of view (for example nonuniform intensity) a stepping series without a sample in the beam—a flat-field—is recorded. The black stepping curves in Fig. 3.3 correspond to this flat-field measurement. The attenuating sample (green) causes a decrease in mean intensity, the curve from the phase-shifting object (red) is shifted sideways and the scattering object (blue) shows a decrease in oscillation amplitude with respect to the unperturbed stepping scan (black).

The recorded stepping curves can be put into equations by describing the stepping scan as a convolution of the reference intensity pattern and the grating transmission function. An idealized intensity pattern (neglecting the extended source) as well as a perfectly absorbing analyzer grating can be described by top-hat transmission functions. The convolution of these functions (movement of one pattern with respect to the other in a phase stepping scan) yields a triangular stepping curve. A convolution of the obtained triangular shape with the projected Gaussian-shaped source yields the recorded nearly sinusoidally shaped intensity pattern. It can be expressed as a constant offset given by the mean intensity \( a_0 \) and modulations, which are described by a series of cosines (Bech,
I (p_x, p_y, x_g) = a_0 (p_x, p_y) + \sum_{m=1}^{\infty} a_m (p_x, p_y) \cos \left( \frac{m x_g}{p_f} 2\pi - \phi_m (p_x, p_y) \right) \tag{3.26}

Higher order terms in m can be neglected unless very small source sizes are used. If the projected source size w is large, i.e. in the order of \( \frac{w}{p_f} > \frac{1}{2\pi} \) the first order term is sufficient (m = 1), as is the case for all grating-based experiments presented in this thesis. In order to accurately determine a first harmonic cosine, a minimum of three measurement positions covering one analyzer grating period is needed.

The parameters \( a_0, a_1 \) and \( \phi_1 \) of the flat-field and sample stepping curve can be extracted from a sine fit to the measured points on the stepping curves. Most often Fourier analysis (using FFT) is used to increase processing speed. Please note that conventional Fourier processing can only be used if the points on the stepping curve are equally spaced over integer multiples of the absorption grating period \( p_2 \).

After having extracted the stepping-curve’s mean value, amplitude and phase parameters in each pixel, we will now discuss how these can be related to the attenuation, refraction and scattering properties of the sample.

### 3.5.4. Attenuation, differential phase and dark-field signal

The stepping curve’s mean value \( a_0 \), amplitude \( a_1 \) and phase \( \phi \) can be related to the attenuation, refraction and scattering properties of the sample. To discriminate data retrieved with and without sample, the subscript \( s \) will denote values extracted from the stepping curve with sample and \( r \) denotes values from the flat-field scan. In the following we use \( x \) and \( y \) instead of \( p_x \) and \( p_y \).

**Attenuation:** The transmission through the sample is given by the ratio of the mean value with sample \( a_{0,s} (x, y) \) to the mean value in the flat-field \( a_{0,r} (x, y) \):

\[
T (x, y) = \frac{I (x, y)}{I_0 (x, y)} = \frac{a_{0,s} (x, y)}{a_{0,r} (x, y)}.
\tag{3.27}

The transmission, \( T \), is related to the projected linear attenuation coefficient \( \mu \) via Beer Lambert law, which is stated in equation 3.9.

**Differential phase:** The extracted phase difference \( \phi_s - \phi_r \) is naturally limited to an interval of \( 2\pi \) and yields the differential phase image:

\[
\Delta \phi (x, y) = \phi_{1,s} (x, y) - \phi_{1,r} (x, y) \tag{3.28}
\]

Combining equation 3.8, 3.10, and 3.25 yields the measured phase shift \( \Delta \phi \) in terms of projected refractive index decrement \( \delta \):

\[
\Delta \phi (x, y) = \frac{2\pi d}{p_2} \frac{\partial}{\partial x} \int_{-\infty}^{+\infty} \delta (x, y, z) \, dz \tag{3.29}
\]

**Dark-field:** Dark-field image contrast is created through changes in the local scattering power of the sample. Small-angle scattering from microstructures with a scale much
smaller than the spatial resolution of the imaging system cause a decrease in visibility of the stepping curve (Pfeiffer et al., 2008; Bech et al., 2012). For homogeneous specimens that show no or negligible small-angle scattering the dark-field signal (relative visibility \( V \)) is close to unity, whereas strong scattering samples yield dark-field signals of \( V < 1 \). The visibility \( V_s \) is calculated from the ratio of amplitude \( a_{1,s} \) to the mean value of the stepping curve \( a_{0,s} \): \( V_s = a_{1,s}/a_{0,s} \). Normalized by the flat-field value \( V_r \) it yields the dark-field or scattering contrast \( V \):

\[
V (x, y) = \frac{V_s (x, y)}{V_r (x, y)}.
\] (3.30)

The dark field signal can be expressed in terms of the material-dependent linear diffusion coefficient \( \epsilon \) and exhibits an exponential dependence on traversed material thickness (Bech, 2009):

\[
V (x, y) = \exp \left( -\frac{2\pi^2 d^2}{p^2} \int \epsilon (x, y, z) \, dz \right).
\] (3.31)

The dark-field signal reveals structural information on the nanometer to hundreds of micrometers scale that is inaccessible from both the absorption and the phase-contrast image (Bech et al., 2010; Chen et al., 2010). Biomedical applications of dark-field contrast include bone imaging (Wen et al., 2009; Potdevin et al., 2012), calcifications in breast imaging (Ando et al., 2005) and tooth imaging (Jensen et al., 2010). Possibilities for analytical calculation and simulation of the dark-field signal are presented in the context of scattering from lung microstructure in section 6.7.

### 3.5.5. Coherence

The grating interferometer has proven to work with polychromatic and extended sources. One parameter that is governed by beam coherence and often used to compare different experimental setups is the interferometer visibility \( V \). The visibility of the flat-field phase stepping curve (or alternatively a Moiré fringe pattern without a sample in the beam) is defined by:

\[
V = \frac{I_{\text{max}} - I_{\text{min}}}{I_{\text{max}} + I_{\text{min}}}.
\] (3.32)

A high visibility is desirable as the error on the measured phase signal decreases with increasing visibility: \( \sigma_\phi \propto 1/V \) (Engel et al., 2011).

The visibility can be reduced by grating production errors but is usually limited due to an extended source size and energy bandwidth of the X-ray source. The effect of both is discussed in the following.

#### Limited spatial coherence

As discussed in section 2.1.3, the transverse coherence is given by the source size and distance from the source to the experiment. In order for interference, e.g. the Talbot effect, to occur, a certain transverse coherence is needed. An upper limit for the source size \( \sigma \) can be deduced from considering the extended source as a sequence of point sources,
which are separated by a distance $\epsilon$. At the interferometer each point source creates an interference pattern, which is shifted by a certain distance up to values where signals cancel out if $\epsilon d/L = p_2/2$. Thus, an upper limit on source size is given by (Bech, 2009):

$$\sigma \leq \frac{p_2 L}{2d}, \quad (3.33)$$

where $L$ corresponds to the distance from the source to the phase grating and $d$ denotes inter-grating distance. Please note that this condition is only required in the direction of sensitivity, i.e. perpendicular to the grating bars. A high degree of spatial coherence is usually provided at synchrotron beamlines and from microfocus tubes, in the latter case a small spot is usually accomplished at the expense of photon flux.

High power X-ray tube sources with extended spot sizes can be used if an additional absorption grating—the source grating—is inserted, which splits the extended source into an array of line sources. Each slit then fulfills the above coherence requirement. The condition for constructive overlap from these individual line sources is given by $p_0 = p_2 \frac{L}{d}$ (Pfeiffer et al., 2006). This geometry is referred to as Talbot-Lau grating interferometer and is the basis for the clinical implementation of the technique.

If the gratings are assumed to be perfectly matched to the X-ray energy, the visibility of the interference pattern is governed by the spatial coherence of the X-ray beam used. The former is put in a relation to the projected source size $w = s \cdot d/L$, by (Weitkamp et al., 2006; Bech, 2009):

$$V\left(\frac{w}{p_I}\right) = \frac{8}{\pi^2} \exp\left(-2\pi^2 \left(\frac{w}{p_I}\right)^2\right). \quad (3.34)$$

The above relation is valid for large sources, which fulfill $w/p_I > 1/2\pi$.

### Limited longitudinal coherence

The grating interferometer is rather insensitive to limited temporal coherence (Weitkamp et al., 2005). It is routinely used with polychromatic sources and exhibits a high visibility over a large range of energies (Engelhardt et al., 2008). In general three effects lead to a decrease in visibility compared to the use with monochromatic sources: (1) the Talbot condition is only met for one wavelength and this condition becomes more strict at higher Talbot orders, (2) the grating only shifts the wavefront by exactly $\pi$ (or $\pi/2$) at the design energy, (3) for higher energies the analyzer grating height might not be sufficient.

The monochromatic spectrum provided by the CLS together with its small source size thus allows for high visibility measurements.

Often, one is interested in the 3D distribution of attenuation, phase-shifting and scattering properties within the sample. Computed tomography (CT), which is a standard tool in attenuation-based imaging, can be used for this purpose and is described in the following section.
3.6. Computed Tomography

Computed tomography (CT) can be used to overcome the main limitation of radiographic images, namely that the information from a three-dimensional object is collapsed on a two-dimensional image plane. CT employs a large set of two-dimensional projection images to reconstruct the three-dimensional information of a sample. This allows to study inner structures in a quantitative and nondestructive way. In medical imaging CT scans are a standard diagnostic tool with a resolution in the order of 500 µm and acquisition times in the order of seconds (Willmott, 2011). The derivations presented in this chapter are adapted from Kak and Slaney (1988).

In a CT scan the sample is rotated around an axis perpendicular to the direction of X-ray beam propagation and most often parallel to the grating bars in the case of GBI. Projection images covering an angular range of 180° are recorded. The number of projections needed to reconstruct the sample is determined by the resolution one wishes to obtain and is given by $N_{proj} = N_p \cdot \frac{\pi}{2}$, where $N_p$ is the number of pixels in one detector row (Willmott, 2011).

In a parallel-beam geometry, the volume can be reconstructed slice by slice along the tomography axis. Thus, the information from one detector row and multiple projection angles—the sinogram—is used for the reconstruction of a single transverse sample slice. The reconstruction of a 2D image from line projections is most commonly solved with the filtered backprojection, which is outlined in the following. Iterative reconstruction schemes have been developed to enhance reconstructed image quality by reducing noise and image artifacts. An example of how phase-contrast CT benefits from the use of iterative reconstruction schemes is provided in section 7. A description of the theoretical basis of iterative reconstruction schemes is beyond the scope of this thesis and the reader is referred to Herman (2010).

3.6.1. The Fourier slice theorem

The Fourier slice theorem states that the Fourier transform of a line projection of a 2D distribution, $f(x, y)$, corresponds to a line in the Fourier transform of $f(x, y)$. This implies that by recording a sufficient number of projection lines, we are filling information on our sample into its Fourier space representation and are therefore able to reconstruct the object, i.e. its 2D distribution. A mathematical description of this approach is given in the following.

Suppose that we have an object function $f(x, y)$ from which we produce a projection along straight lines at an angle $\theta$. We introduce a rotated coordinate system with coordinates $x'$ and $y'$, which is rotated at an angle $\theta$ such that $y'$ is parallel to the projection direction. In this rotated coordinate system, the projection can be expressed as (compare Fig. 3.4):

$$ p_\theta(x') = \int f(x', y') \, dy'. $$

(3.35)

The representation of a function $f(x, y)$, by a set of line integrals $p_\theta(x')$, is called the Radon-transform of this function.
Figure 3.4.: The Fourier slice theorem. An object function $f(x, y)$ is traversed at an angle $\theta$ to yield a projection $p_\theta(x')$ in a rotated coordinate system. The Fourier slice theorem states that the Fourier transform $P_\theta(q_x')$ of $p_\theta(x')$ represents a line in the Fourier space representation, $F(q_x, q_y)$, of the object function $f(x, y)$.

If we consider a projection at an angle $\theta = 0$ this simplifies to:

$$p_0(x) = \int f(x, y) \, dy,$$

and its Fourier transform is given by:

$$P_0(q_x) = \int p_0(x) e^{-i2\pi q_x x} \, dx.$$ (3.37)

In the Fourier transform of the object function $f(x, y)$, with $q_y = 0$, we recognize the expression from equation 3.36:

$$F(q_x, q_y = 0) = \int \left[ \int f(x, y) \, dy \right] e^{-i2\pi(q_x x)} \, dx = \int p_0(x) e^{-i2\pi q_x x} \, dx = P_0(q_x).$$ (3.38)

We have thereby related a line of the object in Fourier space, $F(q_x, q_y = 0)$, to the Fourier transform of a projection, $P_0(q_x)$. The former result is applicable for arbitrarily rotated coordinate systems $(x', y')$ (compare Fig. 3.4) and thus the theorem relating line projection to Fourier space representation is applicable for arbitrary projection angles $\theta$.

### 3.6.2. The filtered backprojection algorithm

The filtered backprojection (FBP) algorithm is the most often used algorithm for the reconstruction of CT data. It is based on the Fourier slice theorem and can be deduced from an introduction of polar coordinates $(w, \theta)$ in the Fourier transform $F(q_x, q_y)$ (Kak and Slaney, 1988):

$$f(x, y) = \int_0^\pi \int_{-\infty}^{+\infty} P_\theta(w) \cdot \frac{|w|}{\text{filter } H(w)} \cdot e^{-i2\pi w s} \, dw \, d\theta.$$ (3.39)
Prior to summing over the contributions from all angles $d\theta$, the projections $p_\theta(s)$ are filtered, e.g. multiplied with a filter function $|w|$ in Fourier space. Filter functions $H(w)$ other than the ramp $|w|$ in equation 3.39 can be used to reduce high frequency image noise; one example is the Ram-Lak filter where a high frequency cut-off is implemented.

The filtered backprojection can be used for the reconstruction of all signals that constitute line projections of an unknown distribution. In the following we will show how absorption and dark-field projections serve to reconstruct object functions $\mu(x,y)$ and $\epsilon(x,y)$ respectively:

**Absorption CT**: The line projection of a sample’s linear attenuation coefficient $\mu$ in a rotated coordinate system can be related to the transmission $T$ (compare equation 3.9):

$$T_\theta(x') = \exp \left[ - \int \mu(x',y') \, dy' \right].$$

(3.40)

Its Fourier transform $\tilde{T}(w) = \mathcal{F}T \{ -\ln T_\theta(x') \}$ can be used in the Filtered backprojection equation 3.39:

$$\mu(x,y) = \int_0^\pi \mathcal{F}T^{-1} \left\{ H(w) \tilde{T}(w) \right\} \, d\theta.$$  

(3.41)

**Dark-field CT**: In analogy to the previous case, the Fourier transform of a dark-field projection (compare equation 3.31):

$$V_\theta(x') = \exp \left[ - \frac{2\pi^2 d^2}{p_2^2} \int \epsilon(x',y') \, dy' \right],$$

(3.42)

is given by $\tilde{V}(w) = \mathcal{F}T \{ -\ln V_\theta(x') \}$ and can be used for the filtered backprojection reconstruction:

$$\epsilon(x,y) = \frac{p_2^2}{2\pi^2 d^2} \int_0^\pi \mathcal{F}T^{-1} \left\{ H(w) \tilde{V}(w) \right\} \, d\theta.$$  

(3.43)

In both cases a Ram-Lak filter, as well as other commonly used filters like the Hamming or Shepp-Logan filter can be used.

At this point, we would like to emphasize that the above rules can be applied also for phase projections if the phase has been retrieved meaning that projection data has been generated. This can be achieved by an integration of differential data (compare section 5 or phase retrieval in propagation-based phase-contrast images (compare section 3.2).

### 3.6.3. Reconstruction of differential data

As stated in section 3.5, the phase signal measured with the grating interferometer is given as the first derivative of the accumulated phase shift. Following the above approach of notation in a rotated coordinate system we obtain (compare 3.29):

$$\alpha_\theta(x') = \frac{p_2}{2\pi d} \phi_\theta(x') = \frac{\lambda}{2\pi} \frac{\partial \Phi_\theta(x',y')}{\partial x'} = - \int \frac{\partial \delta(x',y')}{\partial x'} \, dy',$$

(3.44)

with the refraction angle $\alpha$, the measured differential phase signal $\phi$ and the actual phase front $\Phi$, that results from a projection of the refractive index decrement $\delta$. The
reconstruction can be performed analogous to the previous cases. The Fourier transform \( \check{\alpha}(w) = \mathcal{F}\mathcal{T}\{-\alpha_\theta(x')\} \) is again used as an input to the FBP:

\[
\delta(x,y) = \int_0^\pi \mathcal{F}\mathcal{T}^{-1}\{H(w) \check{\alpha}(w)\}d\theta.
\] (3.45)

The differential nature of the signal is accounted for by using an adapted filter function: a Hilbert filter \( H(w) = i \text{sgn}(w)/2\pi \) (Pfeiffer et al., 2007b). Multiplication with the Hilbert filter in Fourier space corresponds to an integration of the differential projections in real space.

**Tomosynthesis** can be viewed as being a limited-angle case of CT. In breast tomosynthesis the covered angular range comprises typically only 40° and \(~20\) projections. This introduces strong artifacts in the reconstruction as the rule for the number of projections as well as the requirement to sample over 180° are both strongly violated. For the reconstruction of attenuation-based tomosynthesis, advanced algorithms have been developed and proven to reduce these artifacts (Dobbins, 2009). FBP serves as a reference in these studies, which is why we used FBP for the the proof-of-principle tomosynthesis results presented in section 8.3 and 8.4 of this thesis.
Part II.

Experimental setup & Method Development
4. Grating interferometer at the CLS

In this chapter the grating interferometer setup used at the Compact Light Source is described. A scintillation counter was added to the experiment to record small variations in X-ray intensity. The installation of the counter enables intensity normalization of frames where the sample covers the entire field of view and allows for online evaluation of X-ray flux during CT experiments.

This chapter is structured as follows: In section 4.1 interferometer components will be discussed in the order in which they are seen by the X-ray beam. Section 4.2 covers the implementation and evaluation of a scintillation counter.

4.1. Description of the imaging setup

![Diagram](image)

Figure 4.1.: Sketch of the Compact Light Source and the grating interferometer (not to scale). The grating interferometer is located at about 16 m distance from the CLS. Grating parameters and detectors are given in table 4.1

The imaging experiment is located at a distance of about 16 m from the CLS collision point, i.e. the point where X-rays are generated (Fig. 4.1). Depending on experimental configuration the beam crosses approximately 13 m of evacuated tube, four Kapton windows each comprising 125 µm, and air before reaching the grating interferometer. The entire interferometer was not installed permanently and the setup was adapted when sources of instabilities were identified. Fig. 4.2 shows a photograph of the interferometer that was used to record the results presented in this thesis. Measurements were carried out with either 21 keV or 36 keV mean X-ray energy. Corresponding interferometer parameters are summarized in table 4.1.
4.1. Description of the imaging setup

Figure 4.2.: The figure shows the grating interferometer that was temporarily installed at the CLS. The setup comprises a sample stage (I), a phase grating (II), an absorption grating (III), which can be moved with respect to the phase grating via a nanoconverter, and either the PILATUS detector (IV) or the Rayonix detector (V).

Gratings were manufactured by microworks GmbH (Karlsruhe, Germany) and are produced on 500 µm silicon wafers with a circular grating area of 70 mm diameter. We used a π/2-phase shift grating with Ni bars. In both configurations the first fractional Talbot distance was chosen. The visibility of the interferometer is determined by various parameters including source size, grating quality, and the degree to which X-ray energy and grating design energy are matched. The visibility associated with the experimental results shown in this thesis is given in the respective chapters. As can be seen from the mismatch in mean X-ray energy and grating design energy used in our experiments (table 4.1), an increase in visibility is easily achievable through an equalization of the former and thus an improvement of image quality and dose reduction are feasible.

The two gratings were aligned parallel to the tomography axis, i.e. vertically. Fine alignment of the gratings is possible via a rotation of the phase grating through a rotation stage (Goniometer 420, HUBER Diffraktionstechnik GmbH & Co. KG, Rimsting, Germany). A nano-converter, which is driven by a high load motorized actuator (LTA-HL, Newport Spectra-Physics GmbH, Darmstadt, Germany), is used to translate the absorption grating. The nano-converter designed by the Paul Scherrer Institute uses a
mechanical lever arm to reduce translational motion by a factor of 100. To allow for horizontal and transverse sample movements two linear stages (LTM 120-400-HSM, OWIS GmbH, Staufen, Germany) were used. To perform CT scans a rotation stage (DMT 65-DM4-HSM, OWIS GmbH, Staufen, Germany) is available and equipped with a goniometer head for sample alignment. All motors are driven with a controller (ESP301, Newport Spectra-Physics GmbH, Darmstadt, Germany).

At 21 keV mean X-ray energy a photon counting PILATUS 100K detector (Dectris LTD, Switzerland), which comprises a silicon sensor of 450 µm thickness was used. To avoid double counting due to charge sharing effects the threshold of the detector was set to half the X-ray energy in all experiments. The detector comprises 195 pixel x 487 pixel with a pixel size of 172 µm x 172 µm.

At an X-ray energy of 36 keV a Varian PaxScan 2520D with a 600 µm CsI scintillator and square pixels of 127 µm x 127 µm served as X-ray detector. At both energies a Rayonix SX-165 CCD detector (Rayonix LLC, Evanston IL, USA) with a nominal 79.59 µm resolution was used as an alternative if higher spatial resolution was needed. All motor movements in between image acquisitions were in this case not directly synchronized with the detector but rather with the shutter signal from the CLS source exit window. To avoid phase wrapping at the sample to air interface a water bath was used during lung experiments presented in chapter 6.

<table>
<thead>
<tr>
<th>mean X-ray energy</th>
<th>21 keV</th>
<th>36 keV</th>
</tr>
</thead>
<tbody>
<tr>
<td>phase grating</td>
<td>design energy</td>
<td>23 keV</td>
</tr>
<tr>
<td></td>
<td>Ni thickness</td>
<td>4.03 µm</td>
</tr>
<tr>
<td></td>
<td>period</td>
<td>5.3 µm</td>
</tr>
<tr>
<td>absorption grating</td>
<td>gold thickness</td>
<td>min. 55 µm</td>
</tr>
<tr>
<td></td>
<td>period</td>
<td>5.4 µm</td>
</tr>
<tr>
<td>inter-grating distance</td>
<td>278 mm</td>
<td>396 mm</td>
</tr>
<tr>
<td>detector</td>
<td>PILATUS 100K</td>
<td>PaxScan 2520D</td>
</tr>
<tr>
<td></td>
<td>Rayonix SX-165</td>
<td>Rayonix SX-165</td>
</tr>
</tbody>
</table>

Table 4.1.: Interferometer characteristics. The used X-ray energies, grating periods and materials, inter-grating distances and detectors are listed.

4.2. Scintillation counter

Due to the more complex principle of X-ray generation in inverse Compton scattering as compared to a standard X-ray tube, there is the possibility of small X-ray intensity fluctuations due to, for example, collision time jitters or variations in stored optical power in the laser system. A normalization signal is necessary to adjust pixel values of each frame in a phase stepping scan. If the sample does not cover the entire field of view, a region outside the sample can be used for this purpose. If, however, larger samples are considered, this approach does not work. In order to measure small variations in X-ray intensity independently from the imaging process itself, a scintillation detector was placed close to the source (see Fig. 4.3 (a)). The scintillation counter comprises a CsI(Tl)
Figure 4.3.: The scintillation counter measures X-rays scattered from a Kapton window, which serves as an entrance window of the evacuated flight tube, located at about 6 m from the source (a). A raw detector frame recorded with the photon counting PILATUS detector (b). The red rectangle is placed in an area where interference effects have been destroyed by inserting wood in the beam. Mean counts in this area are used for subsequent comparison to the signal obtained from the scintillation counter (c). Both lines match well; indicating that the normalized measurement of samples that cover the entire field of view is possible.

crystal, a photomultiplier and electronics to generate TTL signals (Transistor-transistor logic electric signal) that can be read out with a USB Counter (USB-4301, Measurement Computing). The scintillation counter measures X-rays scattered from a Kapton foil, which serves as an entrance window for the evacuated X-ray flight tube and is placed at approximately 6 m from the source (Fig. 4.1).

In order to test the accuracy of the scintillator signal, we compared it to Pilatus pixel values in a region outside of the sample. In Fig. 4.3 (b) a raw projection image from a mouse CT scan is shown, where interference effects have been destroyed by inserting wood at the left side of the field of view. The red rectangle indicates pixels in the respective area that have been used to calculate mean counts in each image frame. Both, detector exposure time and USB counter time, were set to 10 s where the latter is gated by the counting start and end of the Pilatus detector. The signals are normalized to one and resulting curves comprising 250 image frames are presented in Fig. 4.3 (c). Both signals agree well with each other. Therefore, the use of a scintillation counter allows for quantitative measurements of larger samples in the presence of X-ray flux fluctuations. Furthermore, in order to avoid artifacts, online evaluation of the counter signal is used to repeat projection image measurements in a CT scan if counts on the scintillator are below a preset threshold.
5. Regularized iterative integration

In this chapter a regularized integration algorithm for retrieval of the projected phase from differential phase-contrast measurements is introduced and evaluated in the context of mammography. By applying regularizations that take the sample structure and the noise properties of the acquired signal into account we can avoid loss of information during integration. It was found that the algorithm, if applied prior to a CT reconstruction, can be used to reduce stripe artifacts in sagittal CT views.

This chapter is structured as follows. In section 5.1 a motivation for the use of a regularized integration algorithm is given together with examples of artifacts arising from non-regularized processing approaches. The algorithm itself is introduced in section 5.2, followed by application examples of the technique to phase-contrast mammography and phase-contrast CT in section 5.3 and 5.4 respectively. In section 5.5, the main results and possible alternative approaches to the problem are summarized.

5.1. Motivation

In conventional absorption based mammography, the projected absorption coefficient of the human breast is displayed and used for diagnosis (see Fig. 5.1 (a)). Phase-contrast projections that are recorded with a grating interferometer yield the first derivative of the projected phase (see Fig. 5.1 (b)). Due to the differential nature of the signal, recorded images are not directly comparable to conventional mammography results and thus more difficult to read for radiologists who are used to interpret breast projection images based on X-ray attenuation. The calculation of a projected phase image, $\Phi$, from the measured differential phase $\partial \Phi / \partial x$—termed gradient image $g$—is also known as the phase retrieval step. One straightforward approach is the direct integration of the differential phase signal in each detector line:

$$\Phi = \frac{p_2}{d\lambda} \int_0^x g \, dx,$$

with the absorption grating period $p_2$, X-ray wavelength $\lambda$ and the inter-grating distance $d$. If, however, noise is present in the differential phase image, this noise is added up in the integration process and the result shows severe stripe artifacts (see Fig. 5.1 (c)). Furthermore, an offset value to each line—the integration constant—is unknown, as this value is lost in the differential imaging process. This causes additional stripe artifacts in cases where the sample covers the entire field of view and no pixels are available for normalization. To reduce stripe artifacts generated in a direct integration of differential phase projections, we propose to use a regularized iterative integration algorithm that introduces coupling between detector lines parallel to the grating bars (Thüring et al., 2011).
Figure 5.1: (a) Conventional mammography image of a mastectomy sample slice recorded with a Hologic Selenia Dimension at 25 kVp, 22 mAs, AGD 0.23 mGy. (b) A differential phase projection of the same mastectomy sample, recorded at the CLS. (c) Unregularized integration of (b) leads to severe stripe artifacts in the projected phase.

Figure 5.2: Stripe artifacts in a sagittal view of a phase-contrast CT reconstruction. Small details of the fixated heart sample are obscured by stripe artifacts and overall the image might be perceived as being of poor quality.

As a second example, where coupling between detector lines proves to reduce artifacts, we would like to discuss stripe artifacts in sagittal or coronal CT views as shown in Fig. 5.2. These artifacts stem from the fact that the noise texture in sagittal phase-contrast CT views is highly anisotropic and significantly differs from axial views. The noise power spectrum in differential phase projections is dominated by low frequencies and translates into radially isotropic noise power distribution in axial phase-contrast CT views. As detector lines in a differential phase projection, and thus also slices in a phase-contrast CT reconstruction, are not coupled, the noise power distribution in sagittal and coronal planes is anisotropic with high frequency noise content in the direction along grating bars, corresponding to the observed stripe artifacts. These stripe artifacts can be removed if differential phase projections are integrated with a regularized integration algorithm prior to CT reconstructions.

5.2. Algorithm

In order to retrieve the projected phase image, \( \Phi \), from the measured differential phase, \( g \), iterative regularized integration algorithms are applied to avoid the above described stripe artifacts. Regularization terms, like for example coupling between detector lines,
can be used to reduce stripe artifacts in retrieved phase projections. Compared to direct integration attempts the resulting images are visually more pleasing and yield more accurate quantitative values of the projected phase as specific sample properties can be taken into account in the integration process. We define a cost function \( L \) that is minimized with a non-linear conjugate gradient algorithm (Shewchuk, 1994). This cost function includes the consistency of the solution \( \Phi \) with the measured gradient image \( g \), as well as regularization terms that can be weighted in their relative strength:

\[
L = \sum_{i,j} \frac{1}{\sigma_{i,j}^2} (\Phi_{i+1,j} - \Phi_{i,j} - g_{i,j})^2 + \lambda_1 \sum_{i,j} c_{i,j} (\Phi_{i,j+1} - \Phi_{i,j})^2 + \lambda_2 \sum_{i,j} M_{i,j}^2 \Phi_{i,j}^2.
\]

(5.2)

\( \Phi_{i,j} \) denotes the projected phase image that we wish to reconstruct from our measurements of the differential phase—the gradient image \( g_{i,j} \)—where \( i \) denotes pixel indices normal to the grating bars and \( j \) is the index used to describe different pixels in the direction parallel to the grating bars, e.g. in the direction where gray value variations due to stripe artifacts occur. The first term thus forces our reconstructed solution to be consistent with the measurement we performed. In each pixel this difference is weighted by how trustworthy the measured result is, in other words how large the error \( \sigma_{i,j} \) on the processed differential phase is. We can obtain these uncertainties from advanced processing schemes that simultaneously provide \( \sigma_{i,j} \) and \( g_{i,j} \) (Hahn et al., 2013). Alternatively, \( \sigma_{i,j} \) can be estimated from the error model developed by Engel et al. (2011):

\[
\sigma_{i,j} \propto \frac{1}{V_{i,j} \sqrt{N_{i,j}}},
\]

(5.3)

where \( V_{i,j} \) is the visibility and \( N_{i,j} \) is the total number of photons measured in pixel \((i, j)\).

The second term in Eq. 5.2 minimizes the difference between neighboring pixels along the grating bar direction, \( \Phi_{i,j+1} - \Phi_{i,j} \). The strength of this regularization is depending on the term \( c_{i,j} \), which denotes the inverse of the local variance in the image, which is evaluated in a gaussian window of width \( w \) around the respective pixel \((i, j)\) (Aja-Fernandez et al., 2006). If there are many structures present in the image, the local variance is high and neighboring pixels are allowed to vary by larger amounts and vice versa. The influence of this coupling constraint with respect to measurement consistency and other regularization terms can be tuned by varying the parameter \( \lambda_1 \).

If the sample under investigation does not cover the entire field of view, we can apply a zero background mask \( M \), which we can calculate from the absorption and dark-field projection image. The relative weight of the zero background constraint can be tuned by varying \( \lambda_2 \). The minimization process is stopped either if a predefined maximum number of iterations is reached, or if the stopping condition, which compares the change applied in the current reconstruction step to a tolerance value, is met.
5.3. Differential phase-contrast mammography

Differential phase-contrast projections of a fixated slice of a human mastectomy sample, which were recorded at the CLS (for details on data acquisition compare section 8.4), were integrated using the previously described algorithm. Information from dark-field and absorption image was used to generate a zero background mask. Phase uncertainty values \( \sigma_{i,j} \) were obtained from an advanced processing algorithm (Hahn et al., 2013). We tested various combinations of tunable parameters: width of the region used for local variance evaluation \( w \), coupling strength \( \lambda_1 \) and zero-background constraint \( \lambda_2 \) to obtain an optimum integration result. The best visual appearance was achieved using the following parameters: \( w = 4 \) (given in pixel units), \( \lambda_1 = 10 \), \( \lambda_2 = 10000 \), and a maximum number of 1000 iterations (Fig. 5.3 (b)). In (c) and (d) the result of too low \( (\lambda_1 = 0.1) \) and too high \( (\lambda_1 = 100) \) coupling along the grating bar direction is presented while other parameters remained unchanged. The computation time for the integration of one projection comprising 372×856 pixel\(^2\) is about 50 s (for 758 iterations). A comparison of the optimal result, Fig. 5.3 (b), to an unregularized integration, Fig. 5.3 (a), shows that the algorithm effectively suppresses stripe artifacts. At the same time severe low frequency artifacts are introduced. These arise from the fact that low frequencies are not well defined in differential phase projections. Although the obtained image is already easier to interpret than a differential phase image, additional regularizations might have to be employed to obtain unambiguous diagnostic information. A possible regularization that uses additional information from the absorption image is discussed in the following.

Regularization by adding absorption image content

One option to reduce low frequency artifacts in integrated images is coupling of low frequency absorption, and phase information. A corresponding regularization term, which could be added to equation 5.2, is:

\[
L = \ldots + \lambda_3 \sum_{q_i, q_j} w(q) \left( \alpha \mathcal{F} \{ \ln T_{i,j} \} - \mathcal{F} \{ \Phi_{i,j}/k \} \right)^2,
\]

where \( T_{i,j} \) and \( \Phi_{i,j} \) denote transmission and integrated phase image respectively, and \( q_i, q_j \) are Fourier space coordinates. This regularization term enforces similarity between low frequency components of the projected phase image, which are selected through a weighting function \( w(q) \) and the corresponding low frequency content from the absorption image, where \( \alpha \) is a fixed \( \delta/\mu \)-ratio of the breast sample. By making this assumption we neglect the fact that the attenuation coefficient \( \mu \) is depending on the effective atomic number of the sample through the photoelectric effect. Assuming a fixed value \( \alpha \) throughout the sample is only justified in cases where Compton scattering dominates attenuation and where the variation of effective atomic number \( Z_{eff} \) is small throughout the entire sample. Especially for microcalcifications, which have a significantly higher effective atomic number compared to soft tissue in the breast, this simplification does not hold (Rössl et al., 2012).

\( ^1 \)using a python script on a machine that features four AMD Opteron(tm) 6282 SE processors with 2.6 GHz
Figure 5.3.: Standard integration of a differential phase projection of a mastectomy sample (a), and three regularized integration results using different values for coupling along grating bar direction. The best visual appearance is obtained by using \( \lambda_1 = 10 \) (b). If the regularization parameter is too small, \( \lambda_1 = 0.1 \), stripe artifacts remain (c). If it is chosen too large, \( \lambda_1 = 100 \), image information is washed out along the coupling direction (d). The second row displays a zoom corresponding to the region of interest indicated in (a) for each retrieved phase image.
5.4. Sagittal views of differential phase-contrast CT

Figure 5.4: Variation of coupling parameter $\alpha = \delta/\mu$ in fixated human breast tissue. The ratio $\delta/\mu$ of a breast sample CT scan recorded at 23 keV at the ESRF (details see Sztrókay et al. (2013)) is shown in (a). These values are compared to projected $\alpha$ values calculated from the integrated differential phase and amplitude image from a different breast sample (b). As the range of $\alpha$ values present in the breast tissue does not set a limit on $\alpha$ values in (b), we assume that this ratio can not effectively be used to reduce low frequency integration artifacts.

In Fig. 5.4 (a), we show a phase-contrast CT scan of a fixated human breast specimen, in which values of $\delta/\mu$ vary significantly between different tissue types; in this case fat and tumor. The ratio of $\delta/\mu$ is only useful in the reduction of low frequency integration artifacts, if its minimum and maximum value $\alpha_{\text{min}} = \delta_{\text{min}}/\mu_{\text{max}}$ and $\alpha_{\text{max}} = \delta_{\text{max}}/\mu_{\text{min}}$ in breast tissue set a limit on the $\alpha$ values obtained from integrated projections:

$$\alpha_{\text{min}} = \frac{\Phi_{\text{int}}/k}{-\ln T}_{\text{max}}$$

where a continuous range of $\alpha$ values is created through the superposition of different tissue types. As can be seen in Fig. 5.4, the $\alpha$ values obtained from breast CT data are in a similar range as values that are obtained from the integrated phase and absorption image. A regularization term as proposed in Eq. 5.4 can therefore not be effectively used to reduce low frequency artifacts and maintain quantitative results at the same time.

5.4. Sagittal views of differential phase-contrast CT

Stripe artifacts in sagittal views of phase-contrast CT are linked to the anisotropic noise power as described by Li et al. (2012a). These artifacts pose a severe problem as they hinder the perception of small sample details and introduce errors in quantitative analysis of CT data (Fig. 5.2). In this section we employ regularized integration prior to reconstruction to reduce the stripe artifacts mentioned above. As an example we show a phase-contrast CT scan of a part of a fixated human heart sample, which is used to study
the development of plaque in coronary arteries. We measured the sample in a water-bath at an X-ray tube setup with a three grating interferometer (for experimental setup details, we refer to Willner (2010)). A PILATUS 100K detector (Dectris LTD, Switzerland) with 172 μm × 172 μm pixel size was used to record 1200 phase-contrast projections, which consist of 12 phase steps and an exposure time of 5 s each. The absorption-grating period used was 5.4 μm. Phase uncertainty values $\sigma_{i,j}$ are obtained from an advanced processing algorithm (Hahn et al., 2013) and integration parameters were set to: $w = 2$ (given in pixel units), $\lambda_1 = 1$ and $\lambda_2 = 10$ and a maximum of 500 iterations. The computation time for the integration of one projection (195 pixel × 399 pixel) is about 3 s (for 186 iterations)$^1$. Fig. 5.5 shows a comparison of a standard phase-contrast CT reconstruction using a Hilbert filter and regularized integration prior to FBP reconstruction with a Ram-Lak filter. Sagittal stripes are significantly reduced when using a regularized integration step (Fig. 5.5 (b,e)) and the accuracy of the reconstruction is not deteriorated (see line plots in Fig. 5.5 (c,f)).

$^1$using a python script on a machine that features four AMD Opteron(tm) 6282 SE processors with 2.6 GHz
5.5. Summary and discussion

Compared to attenuation or phase projection images, differential phase-contrast projections are more difficult to interpret and to quantitatively analyze. We showed that the direct—unregularized—integration of differential phase projections results in severe stripe artifacts. To reduce these stripe artifacts and preserve quantitative information at the same time, iterative regularized integration schemes can be employed. We introduced an algorithm that comprises consistency with measured data, coupling in the direction parallel to the grating bars as well as a zero-background constraint. Regularized integration results from a differential phase mammography projection were presented. The results show a significant decrease in stripe artifacts, whereas low frequency artifacts are introduced. We discussed that coupling attenuation and phase information for regularization purposes is unlikely to yield accurate results due to the large range of $\delta/\mu$ values that are present in breast tissue.

Furthermore, regularized integration was successfully used to reduce stripe artifacts in sagittal phase-contrast CT views. In a CT scan of a fixated heart specimen we showed how stripes were effectively removed and feature visibility increased.

Depending on image size the algorithm took 3 to 50 s to integrate one projection. As the algorithm was not optimized with respect to speed we assume that those values can be decreased dramatically in the future.

Alternative solutions for phase retrieval in differential phase projections include the use of 2D gratings (Zanette et al., 2010), or alternatively a second measurement of the phase gradient with the interferometer—or the sample—rotated by 90 degrees (Kottler et al., 2007). With both approaches scan time and applied dose increase significantly, which can be regarded as an impediment with respect to in-vivo or clinical applications. Furthermore, in cases where a rotation of the sample is not possible, a rotation of the interferometer might introduce misalignment of the gratings due to limited precision in motor movements.

An alternative solution to reduce stripes in sagittal phase-contrast CT views is the use of iterative reconstruction schemes that do not reconstruct slice by slice but rather apply regularizations in 3D, e.g., on a number of axial slices at once. Thus, coupling between adjacent slices can be directly modeled in the cost function, describing the reconstruction process. Instead of applying regularizations on a single projection, we can make use of sample information from all projection angles at once to correctly tune regularization strength. An example where iterative 3D regularization is successfully applied to reduce stripe artifacts is presented in section 7.2.2.
Part III.

Results
6. Dark-field imaging of murine pulmonary emphysema

In early stages of various pulmonary diseases such as emphysema and fibrosis, the change in X-ray attenuation is not detectable with conventional chest radiographs. To monitor the morphological changes that the alveoli network undergoes in the progression of these diseases, we use the dark-field signal, which is related to small-angle scattering in the sample. Combined with the attenuation-based image, the dark-field signal enables better discrimination between healthy and emphysematous lung tissue in a mouse model. Main results presented in this chapter have been published in Schleede et al. (2012b), Meinel et al. (2013), and Schwab et al. (2013).

The chapter starts with an introduction to limitations of clinical imaging of pulmonary emphysema and a review of research in the field of phase-contrast lung imaging in section 6.1 and 6.2 respectively. In section 6.3 the murine emphysema model is described as well as lung function measurements and histological slices in section 6.4, which were used to verify our results. Experimental parameters are summarized in section 6.5. Multi-modal projection images of healthy and elastase-induced emphysema lungs are presented in section 6.6. Theoretical considerations on the dark-field signal created by the lung alveoli, which are given in section 6.7, lead to the calculation of a normalized scatter signal. By using normalized scatter images, healthy and emphysematous lung tissue can be discriminated unambiguously. Corresponding images are presented in section 6.8. A discussion of the obtained results together with examples of further experiments are presented in section 6.9.

6.1. Limitations of clinical imaging

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide (Celli et al., 2004; Zvezdin et al., 2009). It is characterized by airflow limitation and lung inflammation as a response to noxious particles or gases, resulting in a progressive deterioration in lung function and health-related quality of life (Minai et al., 2008; Ley-Zaporozhan et al., 2008).

Emphysema is a common component of COPD, in which airway obstruction and aberrant activity of proteolytic enzymes cause irreversible destruction of alveolar walls and enlargement of distal airspaces. A picture of a human lung with healthy—small diameter—alveoli and enlarged emphysematous alveoli is shown in Fig. 6.1 (a). Despite this altered lung morphology, emphysema is difficult to detect with conventional radiographic imaging, as the decrease in lung tissue density caused by emphysema may be too small to be appreciated. Radiographs of the thorax are routinely used to screen patients
6.1. Limitations of clinical imaging

Figure 6.1.: (a) Picture of emphysematous and healthy alveoli in humans. Image courtesy of Encyclopædia Britannica (Encyclopædia Britannica Online). (b) Photograph of an excised, inflated mouse lung. Photograph (b) was previously published in Schleede et al. (2012b).

with suspected COPD for emphysema although it is known that these radiographs lack sensitivity in mild to moderate emphysema. This is due to the fact that mainly indirect signs of lung destruction are observed in radiographs. These indirect signs include focal absence of pulmonary vessels and flattening of the diaphragm, which are not developed in an early state of the disease, where diagnosis and early treatment would be desirable (Litmanovich et al., 2009). Currently, screening for and early diagnosis of COPD and emphysema largely relies on spirometric lung function tests (Soriano et al., 2009), in which both volume and speed of inhalation and exhalation are recorded. Spirometry, however, strongly depends on patients’ cooperation and is unable to localize emphysematous changes within the lung. Assessing the regional distribution of pulmonary emphysema is crucial for clinical decision-making regarding lung volume reduction surgery and insertion of endobronchial valves (Sciurba et al., 2010; Criner and Mamary, 2010). Emphysema imaging has been greatly improved with high-resolution CT (HRCT) but its use is limited by the higher radiation dose applied to the patient (Washko, 2010). Some studies have suggested that MRI may complement CT in the imaging of emphysema (Washko, 2010). However, since MRI is time-consuming, expensive, less available and prone to breathing artifacts, MRI is currently not established in routine imaging of COPD. Direct assessment of micro-structural changes in the alveolar network would be desirable to assess disease progression and monitor therapy, but this can currently only be achieved through histopathology, which requires invasive biopsy. Especially in early stages of the disease, identification, precise quantification, and localization of emphysema through grating-based X-ray projection imaging could significantly improve COPD diagnosis and therapy without the high radiation exposure associated with CT.
6.2. Review of phase-contrast imaging results

Several other groups have demonstrated that phase-contrast imaging can significantly increase the visibility of lung tissue in single projections (Kitchen et al., 2005a; Hooper et al., 2007; Parsons et al., 2008). It has also been shown to improve the diagnostics of pulmonary diseases (Connor et al., 2011). Multiple air-tissue interfaces present in the inflated lung result in a high degree of X-ray phase contrast and low attenuation contrast. Among the phase-contrast imaging methods available, namely interferometric methods, propagation-based methods and analyzer-based methods, the latter two were intensively studied with respect to lung imaging (Jheon et al., 2006; Hooper et al., 2007; Zhang et al., 2011).

In propagation-based imaging (PBI) studies were carried out with mouse, rat, and rabbit lungs, which show a speckled intensity pattern that is attributed to the air filled alveoli acting as aberrated compound refractive lenses (Kitchen et al., 2004). Using a single distance from sample to detector, PBI does not allow a quantitative analysis of lung projections, due to the a priori assumption of a single material object composition (Kitchen et al., 2005b). In addition to a high-brightness X-ray source, a high resolution detector is needed to resolve the refraction-induced interference fringes.

An application of diffraction enhanced imaging (DEI) or analyzer-based imaging (ABI) to mouse lung measurements has been demonstrated by Kitchen et al. (2010). The so-called scatter rejection or extinction contrast is produced at only the peak position of the rocking curve, where the analyzer crystal rejects X-rays from small-angle scattering. With diffraction enhanced peak images, lung tissue can easily be distinguished from the surrounding soft tissue, leading to an improved discrimination between healthy and diseased lung tissue (Zhong et al., 2000; Connor et al., 2011). Comparing single-distance PBI and single-rocking-angle DEI of mouse and rabbit lungs, indicates that DEI yields images of superior contrast than those based on PBI, while both techniques show a significant contrast improvement over conventional attenuation radiographs (Kitchen et al., 2005a). The use of DEI with lab sources suffers from low monochromatic flux and the resulting long exposure times, which are not compatible with in-vivo imaging applications (Parham et al., 2009; Nesch et al., 2009).

In grating-based imaging, attenuation, phase and scattering contributions of the object are clearly separable. Furthermore, the technique supplies a large field of view and has proven to work with polychromatic sources and in cone-beam geometry (Pfeiffer et al., 2008). The dark-field signal is directly related to small-angle scattering and multiple refraction from microstructures with a scale much smaller than the spatial resolution of the imaging system (Pfeiffer et al., 2008; Bech et al., 2012). This reveals structural information on the nanometer to hundreds of micrometers scale that is inaccessible from both the attenuation and the phase-contrast image (Bech et al., 2010; Chen et al., 2010). Biomedical applications of dark-field contrast include bone imaging (Wen et al., 2009; Potdevin et al., 2012), calcifications in breast imaging (Ando et al., 2005; Michel et al., 2013) and tooth imaging (Jensen et al., 2010).

In the following sections first grating-based dark-field imaging results from murine lungs are presented (a photograph of an excised lung is shown in 6.1 (b)). Through its distinct dependency on mean alveolar sizes, the dark-field signal provides valuable information for lung diagnostics. We demonstrate that a combination of attenuation
6.3. Emphysema model and sample preparation

Six- to eight-week-old pathogen-free female C57BL/6N mice (Charles River Laboratories, Wilmington, MA) were used throughout this study. Mice had free access to water and rodent laboratory chow. Pancreatic elastase was dissolved in sterile phosphate-buffered saline and applied orotracheally (100 U/kg body weight). Control mice received 80 ml sterile phosphate-buffered saline.

To assess information on pulmonary function the mice were anesthetized, tracheostomized and connected to a FlexiVent pulmonary function system (Scireq, EMKA Technologies, Paris, France). During the measurement mice were ventilated with an average breathing frequency of 160/min. After a maximal vital capacity perturbation (TLC), a snapshot perturbation maneuver was applied to determine the dynamic compliance of the whole respiratory system according to the single compartment model. Then the forced oscillation technique perturbation maneuvers quick primewave-3, and primewave-8 were conducted, providing tissue elastance (Vanoirbeek et al., 2010). Dynamic compliance reflects the ease with which the lungs can be extended, whereas tissue elastance is related to the elastic recoil of the lungs. Due to the alveolar tissue loss, values of dynamic compliance are expected to increase and tissue elastance is expected to decrease in emphysematous lungs. Clinically relevant parameters of pulmonary function are given in Table 6.1 and Fig. 6.2. The increase in dynamic compliance due to the loss of alveolar and elastic tissue associated with emphysema can be observed. Furthermore, lung function in mice treated with elastase demonstrated a decrease in tissue elastance (Irvin and Bates, 2003; Vanoirbeek et al., 2010). The functional pattern of the mouse respiratory disease model is thus closely related to emphysema in humans.

<table>
<thead>
<tr>
<th>lung sample</th>
<th>dynamic compliance [ml/cm H$_2$O]</th>
<th>tissue elastance [cm H$_2$O/cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1</td>
<td>0.060 ± 0.002</td>
<td>12.07 ± 0.06</td>
</tr>
<tr>
<td>E2</td>
<td>0.0750 ± 0.0009</td>
<td>9.4 ± 0.3</td>
</tr>
<tr>
<td>E3</td>
<td>0.0722 ± 0.0004</td>
<td>9.8 ± 0.3</td>
</tr>
<tr>
<td>C1</td>
<td>0.0338 ± 0.0005</td>
<td>31.2 ± 0.3</td>
</tr>
<tr>
<td>C2</td>
<td>0.0540 ± 0.0007</td>
<td>17.8 ± 0.5</td>
</tr>
<tr>
<td>C3</td>
<td>0.050 ± 0.002</td>
<td>19.9 ± 0.5</td>
</tr>
</tbody>
</table>

Table 6.1.: Lung function measurements. Dynamic compliance reflects the ease with which the lungs can be extended, whereas tissue elastance is related to the elastic recoil of the lungs. Due to the tissue loss in emphysematous lungs, values of dynamic compliance are expected to increase and tissue elastance is expected to decrease. E1-3 and C1-3 denote elastase-emphysema and control mice respectively. This table was previously published in Schleede et al. (2012b).

and dark-field signal, which was developed in the scope of this thesis, leads to improved diagnosis of emphysema from only a single projection.

6.3. Emphysema model and sample preparation

Six- to eight-week-old pathogen-free female C57BL/6N mice (Charles River Laboratories, Wilmington, MA) were used throughout this study. Mice had free access to water and rodent laboratory chow. Pancreatic elastase was dissolved in sterile phosphate-buffered saline and applied orotracheally (100 U/kg body weight). Control mice received 80 ml sterile phosphate-buffered saline.

To assess information on pulmonary function the mice were anesthetized, tracheostomized and connected to a FlexiVent pulmonary function system (Scireq, EMKA Technologies, Paris, France). During the measurement mice were ventilated with an average breathing frequency of 160/min. After a maximal vital capacity perturbation (TLC), a snapshot perturbation maneuver was applied to determine the dynamic compliance of the whole respiratory system according to the single compartment model. Then the forced oscillation technique perturbation maneuvers quick primewave-3, and primewave-8 were conducted, providing tissue elastance (Vanoirbeek et al., 2010). Dynamic compliance reflects the ease with which the lungs can be extended, whereas tissue elastance is related to the elastic recoil of the lungs. Due to the alveolar tissue loss, values of dynamic compliance are expected to increase and tissue elastance is expected to decrease in emphysematous lungs. For each parameter, an average of three measurements per mouse was calculated. Clinically relevant parameters of pulmonary function are given in Table 6.1 and Fig. 6.2. The increase in dynamic compliance due to the loss of alveolar and elastic tissue associated with emphysema can be observed. Furthermore, lung function in mice treated with elastase demonstrated a decrease in tissue elastance (Irvin and Bates, 2003; Vanoirbeek et al., 2010). The functional pattern of the mouse respiratory disease model is thus closely related to emphysema in humans.
Figure 6.2.: Pulmonary function of six mice included in the experiment. For all samples, dynamic compliance and tissue elastance with their respective standard deviation are depicted. In a comparison of elastase-emphysema (red) and control (blue) samples the expected increase in dynamic compliance and reduction in tissue elastance is apparent. Values are given in table 6.1. E1-3 and C1-3 denote elastase-emphysema and control mice respectively. The figure was previously published in Schleede et al. (2012b).

The mouse lungs were excised 28 days after elastase application, inflated with air, and tied up at the trachea (see photograph Fig. 6.1 (b)). The samples were put in formalin filled plastic containers (photograph Fig. 6.4) and measured in a water bath.

6.4. Histology

After the imaging experiment, histology—the gold standard in emphysema diagnosis—was performed on all lung samples to validate our results. After washing to remove parafformaldehyde, lungs were decalcified in 10% EDTA for 5 days. Subsequently, the specimens were dehydrated and embedded in paraffin. Multiple 10\(\mu\)m thin sections were prepared in the coronal plane at intervals of 0.5 mm to obtain representative sections covering the entire organ. Sections were deparaffinized, hydrated, stained using a routine Mayer’s hematoxylin and eosin (H&E) staining protocol, and dehydrated. Sections were scanned at various magnifications to create digital images.

The change in alveoli diameter is well represented in the histological sections (Fig. 8.9) of healthy ((a),(c)) and emphysematous lung samples ((b),(d)). The loss in lung tissue accompanied by a significant increase in mean alveolar diameter is apparent in the 10-fold magnification of emphysematous mouse lung tissue (d). These findings agree well with the distinct signature of emphysematous lungs in the lung function tests (see Table 6.1), which suggested an advanced stage of the disease.

6.5. Data acquisition

Three emphysematous and three healthy mouse lung samples were measured with a two-grating interferometer setup (Fig. 4.1) at the Compact Light Source (CLS). Measurements were performed at a mean X-ray energy of \(E_{\text{mean}} = 36\text{ keV} (\lambda_{\text{peak}} = 0.34\ \text{Å})\).
Figure 6.3.: Histological sections of lung structure in experimental emphysema. Lung samples were embedded in paraffin and stained using a routine Mayer’s hematoxylin and eosin (H&E) staining protocol. (a),(b) and (c),(d) show 2x and 10x magnification of the lung sections respectively. In the control group ((a),(c), lung sample C1), a dense alveolar network is nicely visible whereas the emphysema lung ((b),(d), lung sample E1), displays the expected pathological larger alveoli diameters with a reduced alveoli number. This figure was previously published in Schleede et al. (2012b).
Grating interferometer parameters corresponding to a mean X-ray energy of 36 keV are given in table 4.1. Each dataset consists of a phase-stepping scan of the absorption grating with respect to the phase grating, over one grating period using 16 steps. The exposure time for each phase step was 5 s. To increase statistics and ensure independency from sample orientation with respect to the interferometer, lungs from six different mice were rotated around a tomographic axis recording 11 projections over 180°. Attenuation, phase-contrast and dark-field images were obtained using standard Fourier processing (Pfeiffer et al., 2009). All images were recorded using a Varian PaxScan 2520D detector with square pixels of 127 µm x 127 µm and a CsI scintillator. To account for small X-ray intensity variations, a scintillation detector was placed close to the source, monitoring X-rays scattered from a Kapton foil. The surface entrance dose was calculated based on the measured flux density of \(8 \times 10^6\) photons \(s^{-1} \text{mm}^{-2}\) at 36 keV and the known attenuation coefficient of dry air. Including all phase steps with 5 s exposure time each, the surface entrance dose of one projection sums up to 33.9 mGy, which is significantly higher than the surface dose of 0.25 mGy used in a conventional clinical chest radiograph (Gray et al., 2005). The dose level of this first in-vitro study was not optimized and can be significantly decreased for example by reducing the support thickness of the grating structures (factor 0.8), by reducing the exposure time (factor 0.25), or by using 4 instead of 16 phase-steps (factor 0.25)). Corresponding results that were processed using binned raw data and a reduced number of phase steps are shown in Fig 6.6.

6.6. Imaging results

The photograph in Fig. 6.4 (a) displays six mouse lungs measured in the experiment. A control lung (b) and one elastase-emphysema lung (c) is displayed in all three contrast modalities, respectively. Image contrast is adjusted to give maximum detail readability. In a comparison of attenuation images from both lungs the anticipated transmission increase in the emphysema lung is visible. The clear depiction of the lung in the dark-field signal can be attributed to strong small-angle scattering of X-rays originating from air filled alveolar structures of the fixated lung.

In both cases—dark-field and attenuation image—the obtained projected value of transmission, \(T\), and visibility, \(V\), alone does not allow for a differentiation between healthy and emphysematous tissue. This is due to the fact that measured projection values not only depend on material properties, namely mean attenuation coefficient, \(\mu\), and mean linear diffusion coefficient, \(\epsilon\), but also on absolute thickness of the lung sample at this particular position (compare equation 3.9 and 3.31). Therefore, it is not possible to discern a thick emphysematous sample from a thin healthy sample if the absolute sample thickness is unknown. To circumvent this issue, we propose a combination of transmission and scattering information in a scatter plot (Fig. 6.5). Each point in the scatter plot represents logarithmic transmission and dark-field pixel values of a lung projection. The data of all six lungs each measured at 11 different projection angles is included. The emphysematous lungs (red) show increased transmission with respect to water and reduced scattering, whereas the healthy lungs (blue) exhibit less increase in transmission and more scattering than the emphysema lungs. In this multimodal visualization a clear separation of healthy versus diseased tissue is achieved.
Figure 6.4.: Three elastase and three control mouse lungs where included in the study. The picture shows all six mouse lungs in formalin filled plastic cylinders. The blue (healthy lung, sample C1) and red (emphysematous lung, sample E1) rectangle indicates the samples that are displayed in transmission $T$ with respect to water, differential phase $d\Phi/dx$ and dark field $V$ below. Each scale bar corresponds to 5 mm. This figure was previously published in Schleede et al. (2012b).
Figure 6.5.: Scatter plot of dark-field $\ln(V)$ versus transmission relative to water $\ln(T)$ of all six lung radiographs and the data from 11 projection angles. From this statistical analysis a clear distinction between emphysematous (red) and control (blue) lung tissue is possible. Two black lines represent a fixed ratio of dark-field and transmission values $\ln(V)/\ln(T)$. Pixels in between these curves are used for further image analysis in Fig. 6.8. Histological sections from sample E1 and C1 in 10 fold magnification are inserted (the scale bar corresponds to 500 $\mu$m). This figure was previously published in Schleede et al. (2012b).
6.6. Imaging results

Figure 6.6.: Demonstration of dose reduction through decrease of statistics in an over-sampled dataset. A comparison of dark-field image and scatter plot for single projections of an emphysematous lung is shown employing the full dataset (a) and using only four of the measured 16 phase steps (b). Furthermore, the effect of 2×2 binning (c) and a combination of 2×2 binning and 4 phase steps (d) resulting in 1/16 of the dose reported for the full dataset is shown. The scale bar corresponds to 5 mm. This figure was previously published in Schleede et al. (2012b).
6.7. Theoretical considerations

Our findings are in good agreement with both theoretical and experimental models, where microspheres of well defined sizes have been used to simulate lung tissue (Kitchen et al., 2004). Wave-optical X-ray propagation simulations of 33 keV X-rays through a mouse lung model with average alveolar size of 60 µm yielded an average deflection angle of zero degrees with a standard deviation of 11 µrad (Kitchen et al., 2004). The sensitivity of the grating interferometer can be tuned to specific scattering angles by adjusting inter-grating distance and absorption grating period (Yashiro et al., 2010). From the geometrical parameters of our experimental setup we can expect a large decrease in visibility for diffraction angles in the range of $p_2/d = 13.6 \mu\text{rad}$ (Bech et al., 2010), which matches the simulated angular spread well and accounts for the large decrease in visibility apparent in the lung projection measurements (compare Fig. 6.4).

The influence of sample structural parameters on the visibility has been simulated in Malecki et al. (2012) and can, in the case of randomly distributed spheres of known radius, be calculated analytically (Yashiro et al., 2010). We consider a lung model of air filled spheres embedded in a lung tissue matrix with a fixed sphere volume fraction and increasing sphere radius (as depicted in the sketch next to the scatter plot (Fig. 6.5). The transmission through all samples with identical sphere volume fraction will stay constant. The change in dark-field signal with increasing sphere radius can be calculated using equations derived in Yashiro et al. (2010):

\[
\frac{V}{V_0} \approx \exp\left[-\sigma^2 (1 - \gamma)\right] \quad (6.1)
\]

\[
\gamma = \left(1 + \frac{x^2}{2}\right) \sqrt{1 - x^2} + \left[2x^2 - \frac{x^4}{2}\right] \ln \left[\frac{|x|}{1 + \sqrt{1 - x^2}}\right] \quad (6.2)
\]

\[
x = \frac{np_2}{2a} \quad (6.3)
\]

\[
\sigma^2 \approx \frac{3}{2} V_s t a \Delta \rho^2 r_e^2 \lambda^2, \quad (6.4)
\]

with the Talbot order $n$, the absorption grating period $p_2$, the mean sphere (alveolar) radius $a$, sphere volume fraction $V_s$, sample thickness $t$, classical electron radius $r_e$, electron density difference $\Delta \rho$ and X-ray wavelength $\lambda$. The electron density difference between lung parenchyma and air is $\Delta \rho_e = 3.4997 \times 10^2\text{nm}^{-3}$ (Kitchen et al., 2005b). The volume fraction of alveoli inside the parenchymal tissue is on the order of 0.6. This value can be obtained from alveolar number density within the parenchyma and alveolar volume values reported in Knust et al. (2009). In Fig. 6.7 the dependency of the dark-field signal on alveolar radius for a sample thickness of 7 mm with a constant alveolar volume fraction is presented. As indicated in the figure, a change in sphere diameter from 80 µm, corresponding to the mean alveoli diameter in healthy mice (Irvin and Bates, 2003), to 90 µm results in a 13% visibility increase from $V = 0.23$ to $V = 0.26$. We conclude that subtle changes in alveoli diameter during early stages of emphysema are likely to appear in the dark-field image without any significant signature in attenuation contrast. Furthermore, it should be noted here, that due to the dependency of equation 6.1 on X-ray wavelength $\lambda$, the spectrum of X-rays has to be known in a polychromatic measurement in order to estimate the mean radius of the scattering spheres from the dark-field image.
6.8. Normalized scatter signal

The apparent discrimination of healthy and emphysematous lung tissue in the scatter plot (Fig. 6.5) is visualized in lung projection images through a combination of attenuation and scattering information. The slope of the scatter plot, \( \ln(V)/\ln(T) \), is denoted normalized scatter in the following. It can be expressed in terms of material-dependent parameters, namely linear diffusion coefficient \( \epsilon \) (Bech et al., 2010) and linear attenuation coefficient \( \mu \):

\[
\frac{\ln(V)}{\ln(T)} \propto \frac{\int \epsilon(z) \, dz}{\int \mu(z) \, dz}.
\]

As the lung was measured with respect to water, the denominator \( \ln(T) \) is proportional to the thickness of the lung, e.g. thickness of air crossed by the X-ray beam. Here we assume that the change in attenuation coefficient, \( \mu \), between emphysematous and healthy lung tissue is negligible. As described in the previous section, \( \ln(V) \) strongly depends on the size of the scattering microstructure. The quantity \( \ln(V)/\ln(T) \) thus combines the information on sample thickness from the attenuation image with the scattering information from the dark-field image. Each pixel’s value of \( \ln(V)/\ln(T) \) is then proportional to the mean linear diffusion coefficient \( \epsilon \) of lung tissue crossed by the
Chapter 6. Dark-field imaging of murine pulmonary emphysema

Figure 6.8.: Multimodal projections of three emphysematous lung samples (E1, E2, E3) and three control lung samples (C1, C2, C3). To visualize the apparent differentiation of healthy and emphysematous lungs from the scatter plot (Fig. 6.5) we propose using threshold values on the quotient of the logarithm of dark-field contrast and transmission values $\ln(V)/\ln(T) = -6$ and $\ln(V)/\ln(T) = -1.2$ (black lines in figure 6.5). In single projections, the corresponding pixels within these limits have been superimposed on the conventional transmission contrast image with their color representing $\ln(V)/\ln(T)$. Standard transmission is depicted in the linear grey scale with transmission values (with respect to water) ranging from 1 to 1.35. The material dependent quotient $\ln(V)/\ln(T)$ is displayed in jet colors ranging from -6 to -1.5, where higher values (yellow, red) correspond to lower scattering at similar transmission and thus larger mean alveoli diameter (the scale bar corresponds to 5 mm). This figure was previously published in Schleede et al. (2012b).
Figure 6.9: Ex-vivo mouse in which the lung was inflated with 800 µl of air. The image shows a dark-field projection scaled from 0.0 to 1.0, which was taken at a grating-based X-ray tube setup operated at 28 kVp (Tapfer et al., 2011). The strong dark-field signal from the lung is not significantly degraded by the overlying structures such as the ribs and the spine, indicating improved contrast is obtained by dark-field imaging of lungs, even in-situ. The animal was half covered by a gel (right half of the image) to reduce the scattering signal from the fur. This figure was previously published in Schleede et al. (2012b).

X-ray beam. Accordingly, linear fits to the scatter plots of each lung sample yield higher values of normalized scatter (higher slope values) for emphysematous lungs ($-4.8 \pm 0.2$) than for healthy lungs ($-11 \pm 3$). For visualization purposes we set threshold values of $\ln(V)/\ln(T)$ to a cutoff value of $-6$ to distinguish emphysematous from healthy lung tissue and to $-1.2$ to exclude background pixel values (black lines in Fig. 6.5). Scatter plot data points inside these limits have been plotted with their normalized scatter value overlaid on conventional attenuation projections in Fig. 6.8.

This multimodal visualization leads to a pronounced difference between the three emphysematous and three control lung samples in single projections. Standard attenuation contrast is depicted in the linear grey scale with relative transmission values (with respect to water) ranging from 1 to 1.35 and $\ln(V)/\ln(T)$ is displayed in jet colors ranging from -6 to -1.5, where high values (yellow, red) correspond to lower scattering from the sample at comparable attenuation properties thus revealing larger mean alveoli diameter. In a less severe case of emphysema this visualization could help identifying small regions of affected lung tissue in single projections.

In order to investigate whether this imaging approach is also feasible in the in-situ setting, we performed an additional experiment with an intact mouse imaged post mortem. Fig. 6.9 shows how the strong dark-field signal from the lung is preserved through overlying ribs, spine, skin, and fur.

6.9. Discussion and Conclusion

The change in X-ray attenuation caused by the pathological process of pulmonary emphysema is difficult to detect in early stages of the disease using conventional attenuation-based radiography. In this chapter we presented the first grating-based dark-field images of emphysematous versus healthy lung tissue. A combination of attenuation and dark-
field signal in a scatter plot analysis revealed that healthy and emphysematous lungs yield significantly different signatures. Moreover, with the introduction of the normalized scatter signal the mean alveolar size of the lung tissue under investigation can be obtained from a single projection image. Thus, the regional distribution of emphysema within the lung becomes accessible from one multimodal projection image and yields improved diagnosis without the higher radiation exposure associated with CT. A strong dependence of the dark-field signal on structural changes in the alveolar network has been established. Our findings were confirmed by pulmonary function measurements and by histology sections.

The distinct signature of the elastase-emphysema mice in lung function measurements (table 6.1) is attributed to the advanced stage of the disease and is expected to break down for subtle changes in lung tissue during early stages of emphysema. Detailed studies looking at different stages and regional distributions of emphysema are planned to assess the potential of our method for emphysema staging and its prospect to replace invasive histopathology.

In addition to the proposed improvements in data acquisition and processing (results shown in Fig. 6.6) the surface dose of the experiment can be further reduced through an optimization of the experimental setup, namely thinning of the grating wafers (which currently comprise 1 mm of silicon), optimization of grating design energy and an overall increase in X-ray energy. Shorter exposure times, can be achieved by using single-shot Moiré techniques (Takeda et al., 1982; Momose et al., 2009), where image resolution is reduced, whereas the sensitivity of the dark-field signal to changes in lung structure is not altered.

Further investigations aim at transferring the proposed analysis from isolated lung samples, measured in a water bath, to lung imaging in mice. An ex-vivo dark-field image of an inflated lung in a mouse (Fig. 6.9) shows that the strong dark-field signal from the lung is not significantly degraded by the overlying structures such as the ribs and the spine. Furthermore, it has been demonstrated by Kitchen et al. (2011) that the projected thickness of bone and soft tissue can be extracted from a single differential phase and attenuation projection image of a mouse. These values can be utilized to normalize both transmission $T$ and dark-field $V$ prior to an analysis of the projected lung diffusion coefficient $\epsilon$.

Future work will focus on establishing the applicability of the method to higher X-ray energies, as necessary for human chest radiographs, and with conventional X-ray tubes, where grating-based phase-contrast imaging has already been successfully demonstrated.

First experiments of excised emphysematous lung samples measured at a small animal phase-contrast CT scanner have been published in Yaroshenko et al. (2013) and in-vivo measurements employing the technique described in this chapter are under way. With future improvements in setup components, data acquisition and processing, we expect our approach of combined dark-field and attenuation-contrast X-ray imaging to offer the possibility of early stage emphysema detection in humans and assess its regional distribution without the use of CT.
7. Computed tomography results from the CLS

In this chapter computed tomography results from the CLS are presented. Due to its near monochromatic X-ray spectrum with an energy bandwidth of only 3%, quantitative values of the linear attenuation coefficient and refractive index decrement can be obtained directly from reconstructed gray values without further energy calibration as required for polychromatic CT measurements. Beam hardening artifacts, which are present in polychromatic X-ray tube measurements, are avoided.

This chapter is structured as follows. In a comparison of measurements of a water cylinder both from the CLS and an X-ray tube a reduction of beam hardening artifacts in the monochromatic results from the CLS is demonstrated in section 7.1. These results are based on a publication by Achterhold et al. (2013). A quantitative grating-based phase-contrast CT scan of a fluid phantom is presented in section 7.2.1. Calculated and measured values of the refractive index agree well, indicating the usefulness of the method for medical as well as material science CT applications. A multimodal CT scan of a fixated infant mouse, which demonstrates superior soft-tissue contrast in the phase measurement as compared to the attenuation measurement, is shown in section 7.2.2. The chapter concludes with a summary of the main results in section 7.3.

7.1. Attenuation-based tomography

7.1.1. Advantages of monochromatic CT

The CLS produces a nearly monochromatic X-ray spectrum of 3% energetic bandwidth with a continuously tunable mean energy. In contrast to CT measurements at polychromatic X-ray tubes, results obtained from monochromatic sources show no beam hardening artifacts. Beam hardening artifacts are produced due to the fact that linear attenuation coefficients are not only material- but also energy dependent, meaning a polychromatic X-ray spectrum is changed when passing through the sample. Low energy X-rays are absorbed to a larger extent and as a result of the changing shape of the X-ray spectrum, the measured linear attenuation coefficient becomes dependent on sample thickness. Furthermore, severe streak artifacts appear in the vicinity of strong absorbing structures like bone or metal implants. Artifact-free monochromatic CT measurements in which the reconstructed gray value can directly be linked to sample attenuation properties are desirable to a large number of applications in X-ray imaging. In medical CT, the exact attenuation values of for example bone are used as an indicator for osteoporosis risk assessment (Augat et al., 1998). In material science applications an automated
segmentation of all material components from a CT histogram is of interest, which is only possible if histogram peaks are sufficiently separated and sufficiently narrow.

### 7.1.2. Data acquisition

To demonstrate the advantages of monochromatic CT, we show the measurement of a water-filled polypropylene container (28.2 mm outer diameter) both at the CLS at a mean X-ray energy of 21 keV and at a FR591 rotating anode X-ray tube (BRUKER-Nonius, Delft, The Netherlands) at tube voltages of 20, 30 and 60 kVp and a current of 60 mA. Apart from a beryllium window at the X-ray tube and four Kapton windows at the CLS, no filters were used to change the shape of the X-ray spectrum. The exposure time at the CLS was 1 s per projection and 0.08 s per projection at the X-ray tube (X-ray flux at the CLS was not optimized for this experiment). 360 projections covering 360° and 500 projections covering 360° were recorded at the CLS and at the X-ray tube respectively. In both cases the PILATUS 100K detector (Dectris LTD, Switzerland) was used. Due to the different magnifications present at the respective setups the effective pixel size at the CLS was 166 µm and at the rotating anode 98 µm. Tomographic slices reconstructed from CLS data have been interpolated to be comparable to stronger magnified tube data.

### 7.1.3. Results

In Fig. 7.1 an average of 10 reconstructed slices from the CLS and the X-ray tube at 60 kVp is shown on the same color scale. The CLS result appears flat—displays constant values—in regions where the sample is homogeneous, for example within water, whereas the X-ray tube CT shows strong beam hardening artifacts with a significant change in reconstructed linear attenuation coefficient from outer to inner parts of the sample.

In Fig. 7.2 (a) line plots including all CT measurements at different X-ray tube voltages are presented. The center flat region corresponds to water and the outer ring represents the plastic container. Beam hardening artifacts with a systematic dependence of reconstructed linear attenuation coefficient, \( \mu \), on depth within the sample are clearly visible and most pronounced in case of lower X-ray energies (black curve representing the 20 kVp measurement). Fig. 7.2 (b) displays histogram plots illustrating the above mentioned advantages of monochromatic CT for automated segmentation purposes. In the histogram from CLS data the peaks corresponding to water and polypropylene are significantly narrower as compared to the X-ray tube results. The broadest distribution in reconstructed attenuation coefficient can be seen for the water peaks of the polychromatic datasets.

In Fig. 7.3 (a) and (b) a CT scan of a fixated mouse recorded at the CLS with a mean X-ray energy of 21 keV is presented. Bone structures have been volume rendered to yield a detailed view on ribs, spine and skull structures present in the mouse. The dataset was recorded using a PILATUS 100K detector (Dectris LTD, Switzerland), 360 projections over 180° and an exposure time of 2 s. Considering geometrical magnification and applying 2x2 interpolation of the dataset results in an isotropic voxel size of 83 µm. In a high resolution scan of the mouse’s skull (Fig. 7.3 (c) and (d)) details of the teeth are clearly visible. This data was obtained using a high resolution CCD (Rayonix,
Figure 7.1.: Comparison of two CT reconstructions of a water phantom measured at 60 kVp at a FR591 rotating anode X-ray tube and at the CLS and at a mean X-ray energy of 21 keV. The color scale represents the linear attenuation coefficient ranging from $\mu = 0.00 \text{ cm}^{-1}$ to $\mu = 1.10 \text{ cm}^{-1}$. The data recorded at the CLS is flat in regions where material is homogeneous, whereas the result from the polychromatic tube spectrum shows severe beam hardening artifacts. An average of 10 slices is depicted to increase signal-to-noise ratio. This figure is adapted from Achterhold et al. (2013).

Figure 7.2.: (a) Profile plots through the center of the reconstructed water phantom, measured at 20, 30 and 60 kVp at the FR591 rotating anode X-ray tube and measured at the CLS at a mean X-ray energy of 21 keV. In contrast to CLS data, all reconstructions of linear attenuation coefficient $\mu$ that were recorded with a polychromatic spectrum show a strong dependence on sample thickness. (b) Histogram of reconstructed CT slices, where the curves have been shifted on the frequency axis for better readability. The red curve representing CLS results is significantly narrower as compared to the X-ray tube results. Both (a) and (b) are calculated from the average of 10 reconstructed slices to increase signal-to-noise ratio. This figure is adapted from Achterhold et al. (2013).
USA) with a pixel size of $16\mu\text{m} \times 16\mu\text{m}$ and by taking 145 images over $180^\circ$ with an exposure time of $10\text{s}$ each. Angular sinogram interpolation by a factor of two was applied prior to reconstruction together with binning by a factor of two prior to visualization. Taking geometric magnification into account results in an isotropic voxel size of $31\mu\text{m}$. In both cases a parallel beam FBP algorithm with a Hamming filter was applied for reconstruction.

Both water-phantom measurements and mouse CT data show that the monochromatic nature of the CLS spectrum allows for a direct relation of reconstructed gray value to attenuation properties of the sample under investigation. These quantitative values are of great interest in many fields of X-ray imaging including medicine and material science applications. As opposed to more commonly used monochromatic sources like large-scale synchrotrons, the CLS has the advantage of a smaller size, which is compatible with a home lab.

### 7.2. Grating-based tomography

In this section quantitative CT measurements of linear attenuation coefficient, refractive index decrement and linear diffusion coefficient are presented. The quantitativosness of the obtained results is tested and verified in a measurement of a phantom containing chemically well defined liquids. Calculated data and measurements agree well. Furthermore, a CT scan of a fixated infant mouse is presented to illustrate the increased
diagnostic value of a multimodal CT scan due to improved soft-tissue contrast in the phase images.

7.2.1. CT scan of a fluid phantom

In order to assess the performance of the interferometer installed at the CLS, a well-defined fluid phantom was measured with grating-based CT. The accuracy of the method can be estimated from a comparison of measured linear attenuation and refractive index values with calculated values obtained from known chemical composition and tabulated data.

The fluid phantom

Seven polyethylene tubes filled with chemically well defined fluid and salt combinations of known weight fractions, \(w_i\), served as a fluid phantom (see photograph in Fig. 7.4 (a)). Theoretical values of mass attenuation coefficient of the sample, \((\mu/\rho)_s\), and refractive index decrement, \(\delta_s\), can be obtained through formulas presented in Herzen et al. (2009); Tapfer et al. (2012):

\[
\left(\frac{\mu}{\rho}\right)_s = \sum_i \left(\frac{\mu}{\rho}\right)_i w_i,
\]

\[
\delta_s = \frac{r_e \lambda^2}{2\pi} \cdot \rho_s \sum_i \frac{N_A Z_i}{A_i} w_i,
\]

with X-ray wavelength \(\lambda\), classical electron radius \(r_e\), Avogadro atomic number \(N_A\), atomic mass of the constituent \(A_i\) and total number of electrons of the constituent \(Z_i\) (under the assumption that we are sufficiently far away from absorption edges). All tabulated data was obtained from the online program XCOM, which is supplied by the National Institute of Standards and Technology (NIST, Gaithersburg, USA)\(^1\). Together with a measured sample density \(\rho_s\) (values given in table 7.1), the linear attenuation coefficient is calculated. Calculated values of linear attenuation coefficient and refractive index decrement of all fluids are presented in table 7.2.

Data acquisition

CT scans were performed at a mean X-ray energy of 21 keV (for corresponding interferometer parameters see table 4.1). 200 projections covering 360\(^\circ\) were recorded. One projection comprises 5 phase stepping images covering one grating period with an exposure time of 5 s each. Before, after, and in the middle of the CT scan a total number of 45 flat-fields was recorded. Images were acquired with the PILATUS 100K detector (Dectris LTD, Switzerland) with a pixel size of 172 \(\mu m\times 172 \mu m\). A mean visibility of 37\% was calculated from a flat-field stepping series. Standard Fourier processing was used to generate multimodal projections of the sample, followed by FBP with a Ram-Lak filter for attenuation projections and a Hilbert filter for differential phase projections.

Results

\(^1\)http://physics.nist.gov/PhysRefData/Xcom/Text/intro.html
Figure 7.4.: Photograph of the fluid phantom containing seven different liquids (a). Average of ten reconstructed slices of linear attenuation coefficient $\mu$ (b) and refractive index decrement $\delta$ (c) of a fluid phantom with chemically well defined liquids. Fluids that exhibit strong contrast in the phase signal have similar gray values in the attenuation image and vice versa. The scale bar corresponds to 3 mm. White numbers in the phase-contrast slice indicate fluid sample numbers introduced in table 7.1.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Solution [wt.%]</th>
<th>density $\rho_s$ [g/cm³]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O (demineralized)</td>
<td>0.997</td>
</tr>
<tr>
<td>2</td>
<td>C₃H₈O₃</td>
<td>1.260</td>
</tr>
<tr>
<td>3</td>
<td>C₃H₅O₃(75%)+C₂H₆O(25%)</td>
<td>1.110</td>
</tr>
<tr>
<td>4</td>
<td>C₃H₅O₃(50%)+C₂H₆O(50%)</td>
<td>0.982</td>
</tr>
<tr>
<td>5</td>
<td>H₂O(95%)+NaCl(5%)</td>
<td>1.033</td>
</tr>
<tr>
<td>6</td>
<td>H₂O(90%)+NaCl(10%)</td>
<td>1.069</td>
</tr>
<tr>
<td>7</td>
<td>C₂H₆O(98.75%)+NaCl(1.25%)</td>
<td>0.800</td>
</tr>
</tbody>
</table>

Table 7.1.: Measured density of the fluids in the fluid phantom. Density measurements employing the buoyancy of a gauged glass structure were performed by Arne Tapfer with a high precision scale (Sartorius LA 230 S) and corresponding density values published in Tapfer et al. (2012).
Table 7.2.: Measured and calculated linear attenuation coefficient $\mu_{m/c}$ and refractive index decrement $\delta_{m/c}$. The error margin is calculated from the standard deviation of the respective RoI.

<table>
<thead>
<tr>
<th>Sample</th>
<th>$\mu_m$ [0.1 cm$^{-1}$]</th>
<th>$\mu_c$ [0.1 cm$^{-1}$]</th>
<th>$\delta_m$ [10$^{-7}$]</th>
<th>$\delta_c$ [10$^{-7}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.19 ± 0.23</td>
<td>7.23</td>
<td>5.28 ± 0.10</td>
<td>5.21</td>
</tr>
<tr>
<td>2</td>
<td>7.40 ± 0.19</td>
<td>7.47</td>
<td>6.62 ± 0.08</td>
<td>6.44</td>
</tr>
<tr>
<td>3</td>
<td>6.36 ± 0.20</td>
<td>6.40</td>
<td>5.82 ± 0.10</td>
<td>5.73</td>
</tr>
<tr>
<td>4</td>
<td>5.45 ± 0.22</td>
<td>5.50</td>
<td>5.16 ± 0.08</td>
<td>5.12</td>
</tr>
<tr>
<td>5</td>
<td>9.69 ± 0.22</td>
<td>9.60</td>
<td>5.53 ± 0.13</td>
<td>5.36</td>
</tr>
<tr>
<td>6</td>
<td>12.05 ± 0.32</td>
<td>12.07</td>
<td>5.40 ± 0.13</td>
<td>5.15</td>
</tr>
<tr>
<td>7</td>
<td>6.06 ± 0.24</td>
<td>6.11</td>
<td>4.24 ± 0.11</td>
<td>4.24</td>
</tr>
</tbody>
</table>

Reconstructed slices of the linear attenuation coefficient and the refractive index decrement are displayed in Fig. 7.4, where an average of 10 slices was chosen to improve signal-to-noise ratio. Streak artifacts present in the phase reconstruction stem from strong phase shifts at the multiple plastic-air interfaces within the sample. These can be avoided by using a water-bath to submerge the sample or by using iterative reconstruction schemes, which can suppress signals that originate from strong phase shifting structures (Hahn et al., 2013). In order to compare our CT results to calculated values, the mean value of a 10 pixel×10 pixel region of interest (RoI) and its respective standard deviation was calculated for each substance in the reconstructed slices shown in Fig. 7.4 (b), (c). A summary of all values can be found in table 7.2. Calculated and measured results match well, apart from a maximum deviation of 1% in the linear attenuation coefficient, which is within the error margins of the measured values, and a maximum mismatch of 5% in refractive index decrement, which might be attributed to the above mentioned streak artifacts. This is further illustrated in a scatter plot in Fig. 7.5 containing $\mu$ and $\delta$ values from every single pixel within our regions of interest as well as the calculated values, which are displayed as a large black triangles. Substances that overlap in their attenuation values are separated in phase contrast and vise versa, indicating that materials with similar attenuation or similar refractive index decrement value can only be distinguished from the simultaneous measurement of both signals.

We conclude, that the additional phase information obtained from grating-based CT supplies unique quantitative information that results in a higher specificity of the measurement and is useful in both medical and material science research.

7.2.2. CT scan of a fixated mouse

To illustrate the superior soft-tissue contrast present in phase-contrast CT as compared to attenuation contrast alone, a formalin fixated infant mouse was measured at the CLS.

Data acquisition and FBP reconstruction

The mean X-ray energy during the experiment was 21 keV (corresponding interferometer parameters are given in table 4.1). We recorded six phase stepping images covering one grating period, where the first and the last images of the stepping series were identical.
and one was omitted in the processing step. We used a Mar CCD detector (Rayonix, USA) with a nominal resolution of 79.59 µm and an exposure time of 8 s per image. A mean visibility of 42% was calculated from a flat-field stepping series. A total number of 45 flat-field images were recorded before, after, and in the middle of the CT scan, which covered 0 to 180.5° in 0.5° steps. As the detector was not interfaced with our measurement software all motor movements were synchronized with the CLS exit window shutter signal.

Resulting sagittal views are presented in Fig. 7.6, showing: linear attenuation coefficient (a), refractive index decrement (b,c) and linear diffusion coefficient (d). Soft-tissue features like the heart of the mouse and the liver are only visible in phase CT data (b,c) and not visible in the attenuation data (a). Below, an axial view at the position of the mouse’s heart is presented in all modalities.

**Iterative reconstruction of phase-contrast CT data**

In addition to conventional FBP with a Hilbert filter, we applied an iterative reconstruction scheme to reduce stripe artifacts and noise in the reconstructed phase-contrast images. Resulting CT views are included in Fig. 7.6 (c). The iterative algorithm takes the statistical properties of image noise into account and allows for various regularizations, which are applied in 3D, meaning that coupling between different axial slices is possible (Hahn et al., 2013). In order to retrieve uncertainty values for each pixel in a differential phase projection, an analytical weighted least square minimization was used for processing. This processing yields, in accordance with the Fourier processing routine,
Figure 7.6.: Grating-based CT measurement of a formalin fixated infant mouse, yielding quantitative values of linear attenuation coefficient $\mu$ (a), refractive index decrement $\delta$ (b),(c) and linear diffusion coefficient $\epsilon$ (d). In (c), an iterative reconstruction scheme (Hahn et al., 2013) was used to reduce stripe artifacts and noise present in the FBP reconstruction of phase-contrast data (c). The scale bar corresponds to 2 mm.
attenuation, differential phase and dark-field values in each pixel plus their corresponding uncertainties, which are propagated from the initial Poisson counting statistics in each pixel: \( \sigma_I = \sqrt{I} \). Reconstruction is performed through the optimization of penalized weighted least squares. We used 25 iterations and a Huber regularization with a weighting factor of \( \lambda = 10^{-5} \) and \( \gamma = 0.01 \). Compared to the standard FBP reconstruction (Fig. 7.6 (b)), we can see that stripe artifacts, which are inherent to sagittal views of grating-based phase-contrast CT (see chapter 5), and artifacts stemming from strong phase shifting structures like bone are successfully reduced with iterative reconstruction schemes Fig. 7.6 (c).

7.3. Summary

In this chapter we demonstrated that attenuation-based CT benefits from the use of monochromatic X-ray sources. As opposed to polychromatic X-ray tube measurements in which beam hardening artifacts pose a severe problem for image interpretation and quantitative evaluation, gray values obtained in attenuation CT at the CLS can directly be used to assess sample attenuation properties. The small X-ray energy bandwidth of 3% results in narrow peaks in the reconstructed histogram and allows for straightforward segmentation of the obtained CT volume.

In grating-based CT measurements of a fluid phantom the quantitative performance of the setup was evaluated in a comparison of measured to calculated values of linear attenuation value and refractive index decrement. It was found that calculated and measured values agree well. Improved soft-tissue contrast in phase images was demonstrated in a CT scan of a fixated infant mouse, in which the heart and the liver of the mouse are only visible in the phase image and not in the attenuation image.
Chapter 8. Phase-contrast mammography and tomosynthesis

8. Phase-contrast mammography and tomosynthesis

In this chapter we will address two issues in mammography, which are accounting for the technique’s often cited low sensitivity and specificity: low attenuation contrast between soft-tissue components of the breast and summation artifacts due to overlapping structures. First, phase-contrast projections of a mammography phantom study at the CLS are presented. The study shows an increase in diagnostic value through enhanced soft-tissue contrast in the differential phase images and scattering information from the dark-field projections as compared to attenuation contrast alone. These results were published in Schleede et al. (2012a). Second, we evaluated phase-contrast tomosynthesis measurements of fixated breast tissue, recorded both at a synchrotron beamline, ID19 ESRF, and at the CLS. The depth resolution in phase-contrast tomosynthesis results in an increase in diagnostic value as compared to single phase-contrast projections. Tomosynthesis results from the ESRF have been submitted for publication by Schleede et al. (2013).

The chapter is structured as follows: In section 8.1 an introduction to limitations of clinical breast imaging is given together with related research attempts in the field of phase-contrast imaging and a motivation for the use of the CLS in breast imaging. Experimental results from a mammography phantom study at the CLS are presented in section 8.2, including a description of mean glandular dose calculation. Phase-contrast tomosynthesis results of fixated breast tissue are presented in the following sections: First, synchrotron benchmark results are presented in section 8.3. Second, these results are compared to dose compatible tomosynthesis measurements preformed at the CLS in section 8.4.

8.1. Motivation

Breast cancer is the most frequently diagnosed cancer and the second leading cause of death among women both in developed and developing countries. Mammography is currently the standard imaging approach for breast cancer screening and has proven to decrease mortality rates due to early cancer detection (Kamangar et al., 2006; WHO, 2008). Besides the technique’s unmet ability to depict microcalcifications, which are an indication in about 30% of breast tumors, there are some drawbacks to mammography with regard to screening purposes: high false positive rates, a high rate of missed cancers, and the X-ray dose received by the patient, which has to be as low as possible in a screening setting. To illustrate the difficulties in the interpretation of attenuation-based projections, we compare mammography images from two patients with histologically proven breast cancer in Fig. 8.1 (images adapted from Grandl et al. (2013)). The can-
8.1. Motivation

Figure 8.1.: Conventional clinical mammography. The cancerous region in (a) (an ACR II breast, meaning relatively low glandular content) is rather easy to depict as opposed to the marked carcinoma in (b) (a rather dense breast, ACR III). Images are adapted from Grandl et al. (2013)

cancerous region in a breast with low glandular tissue fraction (rated ACR II) shown in (a) is rather easy to depict, as opposed to the marked cancerous region in (b), which is easily missed due to the strong white background originating from glandular tissue (rather dense breast, rated ACR III).

These difficulties in breast cancer diagnosis are related to two main limitations in mammography: (1) low attenuation contrast between glandular and tumorous tissue, which results in the techniques reliance on the depiction of lesion margins rather than their gray value differences in the mammogram, and (2) the obscuration of these margins by summation effects. Both issues will be addressed separately in the following paragraphs.

Limited soft-tissue contrast
Apart from microcalcifications, which are made up of high atomic number elements and produce good attenuation contrast, the breast mainly contains soft-tissue components like fat, glandular tissue and potentially tumors, which exhibit very low attenuation contrast. As these small differences in attenuation values are further decreasing with increasing X-ray energy, mammographic exams are made at low energies, resulting in a higher dose applied to the patient.

Elements with a low atomic number Z produce very weak X-ray attenuation but considerably higher phase signal (Momose et al., 2001), therefore phase-contrast imaging techniques have the potential of reducing radiation dose and increasing sensitivity at the same time. Several methods have been developed to measure this phase shift and
promising results in breast projection imaging have been achieved with free space propagation techniques (Arfelli et al., 2000) including a first clinical trial of synchrotron phase-contrast mammography (Castelli et al., 2011). Also analyzer-based imaging (Keyriläinen et al., 2005; Bravin et al., 2007), where dark-field imaging (DFI) of a mammography phantom demonstrated higher detail visibility compared to images from a conventional X-ray tube source (Ando et al., 2005), and interferometric methods (Takeda et al., 1998; Stampanoni et al., 2011; Anton et al., 2013) are available. In this context, grating interferometry is often described as one of the most promising phase-contrast technique for a clinical implementation as it has been proven to work with conventional laboratory X-ray sources (Pfeiffer et al., 2006). This is due to its toleration of divergent, polychromatic X-ray beams and large X-ray source sizes; properties inevitable for sources that yield high enough flux to result in clinically tolerable exposure times.

Superposition artifacts
One possibility to increase the diagnostic value of breast imaging exams and to overcome the problem of tissue overlap inherent to X-ray projection techniques is the application of tomographic approaches. Mass detection in mammography relies mainly on the discrimination of structural disorders, which can be significantly hindered by fibroglandular tissue overlap in a 2D projection technique. This so called ‘anatomical noise’ is a severe problem especially in dense breasts where summation effects can both lead to obscuration of tumors in mammograms and false positive diagnosis (O’Connell et al., 2010).

Currently different approaches are used to supply depth resolution in follow up diagnostic breast imaging, namely ultrasound and contrast enhanced MRI. Compared to X-ray imaging MRI has the clear advantage of avoiding ionizing radiation with the drawbacks of lower spatial resolution, which hinders the detection of microcalcifications, the use of contrast agents, considerable time and effort required, and a low specificity. Ultrasound is highly time-consuming, depends on the operators’ experience and thus results are only partly reproducible (Le-Petross and Shetty, 2011).

In the field of X-ray imaging both breast CT and tomosynthesis are investigated as possible diagnostic and breast cancer screening modalities, where in the latter case the techniques have to compete with the established mammography exam in terms of sensitivity, specificity, interpretability, dose compatibility and cost efficiency.

Unlike CT, tomosynthesis uses only a sparse number of projection angles to produce a quasi 3-D aspect of the object. The technique is currently applied in addition to conventional mammography to reduce the masking of tumors by superposition artifacts (Diekmann and Bick, 2011). In breast CT measurements the trade off between resolution and dose hinders a clear depiction of microcalcifications (Kalender et al., 2012), whereas overlying soft-tissue structures are successfully resolved leading to a superior performance in detecting masses compared to mammography (Lindfors et al., 2008; O’Connell et al., 2010). Contrast-enhanced breast CT showed an improved conspicuity of malignant lesions (Prionas et al., 2010).

Tomosynthesis slices of the breast are reconstructed from a set of 10 to 25 projection images taken over an angular range of often less than 40°, where exact acquisition parameters are part of ongoing research (Dobbins, 2009). Due to the incomplete angular sampling the technique does not supply the isotropic 3D spatial resolution as CT, never-
theless it yields a high spatial resolution in in-plane views comparable to mammography and superior to CT (Boone et al., 2001). The advantages of tomosynthesis compared to standard mammography comprise a better visibility and delineation of masses (Teertstra et al., 2010; Gennaro et al., 2010), which is important for the discrimination of benign and malignant tumors as well as for the discrimination of superposition artifacts and real existing mass lesions. Furthermore the technique offers more accurate 3D localization of masses potentially helpful in biopsy guidance and operation planning. A recent study has demonstrated that the combined use of mammography and tomosynthesis leads to a decrease in false positive diagnostics and a significant increase in cancer detection rate especially in dense breasts (Skaane et al., 2013). The detection of microcalcifications in tomosynthesis is different from mammography due to the possibility that slices of microcalcification clusters are visualized instead of projections of the entire cluster, which are well established in mammography readings (Dobbins, 2009). To circumvent this issue and possibly omit the mammography exam the use of synthetic projection images, calculated from the tomosynthesis dataset are currently discussed and studies are under way to investigate sensitivity and specificity when using tomosynthesis alone—as compared to tomosynthesis in addition to conventional mammography—in breast cancer screening. However, one has to keep in mind that unlike the well established clinical procedure of mammography, in tomosynthesis, studies on acquisition parameters, special training on image interpretation and image post processing are still developing.

In the field of phase-contrast imaging there have been various reports on improved tissue discrimination in phase-contrast CT. In analyzer-based imaging dose compatible results of breast phase-contrast CT have recently been reported (Zhao et al., 2012); grating-based phase-contrast CT measurements of breast tumor tissue revealed improved soft-tissue contrast and better differentiation of tumor types as compared to conventional attenuation-based CT (Sztrókay et al., 2013). These results were obtained at a synchrotron source.

Only few reports on phase-contrast tomosynthesis experiments can be found in the literature, including experiments based on free-space propagation (Hammonds et al., 2011; Wu et al., 2012), analyzer-based methods (Shimao et al., 2007; Maksimenko et al., 2007) and grating interferometry (Wang et al., 2008). In these studies mostly phantoms have been measured to demonstrate both the possibility to separate superimposed objects and the complementarity of phase and attenuation images (Li et al., 2012b).

Breast imaging at a compact synchrotron source
As both phase propagation effects as well as analyzer-based imaging methods yield the best results with high monochromatic flux and spatial coherence, benchmarking experiments in multimodal breast imaging have been carried out at synchrotron sources (Fitzgerald, 2000; Momose, 2003). However, the large size of synchrotron radiation facilities combined with their costs raises doubts on the feasibility of applying these methods to a large number of patients in mammography screening programs. A compact Compton-based synchrotron source, such as the CLS, therefore presents an alternative, as it meets the criteria of clinical compatibility and still provides X-rays of high flux, narrow bandwidth, and spatial coherence. The combination of high flux and a small source size of less than 50 \( \mu \text{m} \times 50 \mu \text{m} \) rms constitutes a considerable advantage compared to conventional mammography, where a compromise between motion blurring and
geometrical blurring associated with large X-ray tube focal spot sizes has to be found. Microfocus X-ray tubes are limited in flux due to the heat load on the target material and thus lead to an increase in overall exposure time (Funke et al., 1998; Koutalonis et al., 2008). At the CLS the high degree of spatial coherence can be exploited in the straightforward use of refraction-based imaging techniques. The intrinsic energy bandwidth of $\Delta E/E_{\text{peak}} = 3\%$ allows for monochromatic mammography, which has proven to yield better results compared to polychromatic radiation (Moeckli et al., 2000; Lawaczeck et al., 2005).

In the following sections we present grating-based phase-contrast mammography phantom measurements from the CLS (section 8.2), as well as diagnostically relevant depth resolution obtained from phase-contrast tomosynthesis of fixated breast tissue (section 8.3 and 8.4).

### 8.2. Mammography phantom

_In this section we show the first multimodal X-ray imaging experiments at the Compact Light Source at a clinical X-ray energy of 21 keV. Dose compatible measurements of a mammography phantom clearly demonstrate an increase in contrast attainable through differential phase and dark-field imaging over conventional attenuation-based projections. The results have been published in Schleede et al. (2012a)._

The section is structured as follows: Details on data acquisition and processing can be found in 8.2.1. Imaging results are presented in 8.2.2; followed by a brief description of dose calculation in 8.2.3. The section concludes with a short summary and outlook in 8.2.4.

#### 8.2.1. Data acquisition

All measurements were made at a clinically compatible X-ray energy of 21 keV ($\lambda_{\text{peak}} = 0.59 \text{ Å}$) and corresponding interferometer parameters can be found in table 4.1. Each dataset consists of a phase stepping scan of the absorption grating with respect to the phase grating over one grating period using 32 steps. The exposure time for each phase step was 5 s resulting in a total exposure time of 160 s. The flat-field image serves as a reference frame to account for local changes in intensity, curvature and coherence of the X-ray beam. The effect of the sample on the wavefront is then calculated using Fourier analysis, resulting in three different contrast modalities (Pfeiffer et al., 2009): standard attenuation, phase-contrast and dark-field images. All images were recorded using a PILATUS detector with square pixels of 172 $\mu$m x 172 $\mu$m. From the flat-field images an average flux of $9.76 \times 10^{5}$ photons/mm$^2$s has been estimated taking the efficiency of the detector, the attenuation of the two gratings and surrounding air into account. The PILATUS detector efficiency is determined by the absorption of the 450 $\mu$m thick silicon sensor at 21 keV. The Mammographic Accreditation Phantom (Gammex Model 156) approximates 4.2 cm of compressed breast. It is made up of a wax block containing 16 test objects (Fig. 8.2) including different sizes of nylon fibers, which simulate fibrous structures, tumor-like masses and groups of simulated micro-calcifications.
8.2.2. Multimodal projections

Next to the sketch of the phantom geometry (Fig. 8.2) the mammography phantom is displayed in all three contrast modalities. Image contrast is adjusted to give maximum detail readability. Six projections have been stitched together to cover the entire mammography phantom. It is important to note that the field of view is limited by the active area of the PILATUS detector of 8.38 cm x 3.35 cm and the grating area with a diameter of 7 cm.

![Figure 8.2: The sketch displays the location of the test objects in the Mammographic Accreditation Phantom and their position in relation to the notched corner of the wax block. The attenuation, differential phase-contrast and the dark-field images are shown. Each image displays six images stitched together, resulting in a total field of view of 8.0 cm x 8.1 cm. This figure was previously published in Schleede et al. (2012a).](image)

A comparison of the detectability of the test objects in the different contrast modalities demonstrates that the phase and the dark-field image provide additional information to the conventional attenuation image. The small nylon fibers (test object five and six in Fig 8.2) are not visible in attenuation and dark-field image, but are clearly visible in the phase-contrast image. All tumor-like masses, test objects 12, 13, 14, 15 and 16, appear more visible in the dark-field image compared to the attenuation image. The smallest tumor-like mass in the phantom, test object 16, is not visible in the attenuation-contrast image and is thus only detectable by use of the dark-field image. The large difference in scattering strength from tumor-like masses 15 compared to 14 indicates a variation in material homogeneity not obvious from the attenuation image.

Figure 8.3 shows imaging results of selected test objects of the Mammographic Accreditation Phantom including line plots of attenuation, differential phase and dark-field values that can be used to quantitatively compare the different contrast modalities. The line plots corresponding to the nylon fibers were calculated by integrating pixel values along the direction of the nylon fiber over the region indicated by colored rectangles. Both nylon fibers (test objects 2 and 6) are significantly better visible in the differential phase-contrast image. In case of the tumor-like mass (test object 16) and the micro-calcifications (test object 9) the plot displays one line through the original image indicated by a color bar. Simulated micro-calcifications and tumor-like masses appear more visible in the phase-contrast and the dark-field image. The line plots of attenuation signal (blue) and dark field signal (green) demonstrate a significant increase in contrast-to-noise ratio (CNR) in the dark-field image.
Figure 8.3: Test objects 2 (1.12 mm nylon fiber), 6 (0.40 mm nylon fiber), 9 (0.32 mm simulated micro-calcification) and 16 (0.25 mm thick tumor-like mass) of the Mammographic Accreditation Phantom (Figure 8.2) are shown in conventional attenuation $I/I_0$, differential phase contrast $\phi - \phi_0$, and dark-field contrast $V/V_0$. Color bars in the images indicate sections, where line plots of the contrast signal have been extracted. This figure was previously published in Schleede et al. (2012a).
Fig. 8.4 shows attenuation and dark-field imaging results of test object 15 (0.50 mm thick tumor-like mass) recorded by using a mean glandular dose of 1.09 mGy (4 phase steps). The reduction in dose has been achieved by processing only four of the 32 recorded phase steps. As the exposure time of each phase step remained constant throughout the experiment this approach results in a reduction of dose and exposure time by a factor of eight. A comparison of the tumor-like mass in attenuation and dark-field contrast demonstrates superior tumor detectability in the dark-field image using less than the single-view mammography clinical dose (NCRP, 2004). A dedicated CNR analysis of the attenuation and dark field signal of test object 15 is displayed in table 1. The CNR values have been calculated in an area of 14 x 11 pixel in the tumor-like mass and the surrounding material pixels respectively:

\[
CNR = \frac{|S_a - S_b|}{\sqrt{\sigma_a^2 + \sigma_b^2}},
\]

where \(S_a\) and \(S_b\) represent the mean value of the signal in region a and b and \(\sigma_a\) and \(\sigma_b\) correspond to the standard deviations of the respective signals. A superior detectability of the test object in the lowest dose (4 phase steps) dark-field image compared to the 32 phase steps (maximum dose in the experiment) attenuation-contrast image has been achieved. These results indicate the potential for further reduction in dose through the use of multimodal imaging techniques without decrease in image quality and tumor detectability. Furthermore it should be noted here that all other tumor-like masses in the phantom show a less distinct difference in the CNR of dark field and attenuation signal, which has to be attributed to different scattering strengths and thus differing microstructure of the materials used to create the tumor-like masses in the phantom. This implies that there is a need for dedicated phase-contrast and dark-field mammography phantoms, which allow for a detailed comparison of breast imaging techniques that exploit refraction and scattering effects of X-rays in tissue.

8.2.3. X-ray dose estimate

The Mammographic Accreditation Phantom (Gammex Model 156) approximates 4.2 cm of compressed breast. We assumed a 50% glandular and 50% adipose by weight breast
Table 8.1.: Contrast-to-noise-ratio (CNR) of selected regions of the attenuation and dark-field images of a tumor-like mass (test object 15). As the exposure time of each phase step remained unchanged during the experiment, a reduction in number of processed phase steps results in a lower dose to the phantom. Please note that the low contrast-to-noise-ratio ($CN_{att} < 1$) of the attenuation signal corresponds to a noise level that is higher than the difference in mean pixel values and therefore does not allow for tissue discrimination in the image. This table was previously published in Schleede et al. (2012a).

<table>
<thead>
<tr>
<th>Number of phase steps</th>
<th>$CN_{att}$</th>
<th>$CN_{df}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.1</td>
<td>4.7</td>
</tr>
<tr>
<td>8</td>
<td>0.1</td>
<td>6.5</td>
</tr>
<tr>
<td>16</td>
<td>0.1</td>
<td>9.2</td>
</tr>
<tr>
<td>32</td>
<td>0.1</td>
<td>12.8</td>
</tr>
</tbody>
</table>

tissue composition with an outer 0.5 cm thick adipose layer as proposed in NCRP, 1986. Values of mean glandular dose in a monochromatic experiment have been calculated according to the method of Arfelli et al. (1998), where glandular dose $D_g$, at depth $x$ in the sample is calculated from X-ray flux $\phi$ (given in $N_{\text{photons}} \, s^{-1} \, mm^{-2}$), X-ray energy $E_x$, adipose tissue attenuation coefficient $\mu_a$, glandular-adipose mixture attenuation coefficient $\mu_m$, glandular tissue attenuation coefficient $\mu_{en,g}$, and glandular tissue density $\rho_g$:

$$D_g(x) = \frac{\phi E_x \mu_{en,g}}{\rho_g} \exp[-\mu_a t_s - \mu_m (x - t_s)].$$

(8.2)
The mean glandular dose (MGD) applied to a breast of thickness $t$ with an outer adipose skin layer of $t_s = 0.5 \, cm$ can be calculated by integrating equation 8.2:

$$\text{MGD} = \frac{1}{t - 2t_s} \int_{t_s}^{t-t_s} D_g(x) \, dx.$$ 

(8.3)

Values of tissue attenuation properties have been approximated with data corresponding to an X-ray energy of 20 keV, published by Dance et al. (1999), yielding $\mu_a = 0.512 \, cm^{-1}$ and $\mu_{en,g}/\rho_g = 0.509 \, cm^2 g^{-1}$. The value of glandular-adipose mixture attenuation has been calculated using equation 7.1 for mixtures of known weight fractions and the corresponding values of attenuation and density for glandular and adipose tissue respectively: $\rho_a = 0.93 \, g \, cm^{-3}$, $\rho_g = 1.04 \, g \, cm^{-3}$ and $\mu_g = 0.794 \, cm^{-1}$, yielding $\mu_m = 0.645 \, cm^{-1}$. From a series of flat-field images an average flux of $9.76 \times 10^5 \, \text{photons/mm}^2 \, \text{s}$ has been estimated taking photon counting detector efficiency, attenuation of two gratings and surrounding air into account. The dose of this proof-of-principle experiment sums up to $8.75 \, \text{mGy}$ for the full dataset (as displayed in Fig. 8.2) and is higher than the upper dose limit for single-view mammography of 3 mGy (NCRP, 2004). It can be significantly reduced through thinning of the grating wafers (which currently comprise 1 mm of silicon) and improved detector efficiency at 21 keV. Dose compatible results are shown in Fig. 8.4, where a reduced number of phase steps and thus shorter overall exposure times (20s) have been used. The combination of more efficient X-ray detection after penetra-
tion of the sample and an expected increase in overall flux from the X-ray source will further reduce the exposure time down to clinically compatible values.

8.2.4. Summary

The standard Mammographic Accreditation Phantom (Gammex 156) has been measured in a first proof-of-principle experiment at a compact synchrotron light source using a grating-based interferometer. We achieved a better detectability of all test objects by combining the complementary information of attenuation, differential phase-contrast and dark-field images. By focusing on single test objects in the phantom, enhanced contrast of differential phase and dark-field signal compared to the conventional attenuation image has been demonstrated. Dose compatible dark-field measurements with high CNR of tumor-like masses have been shown. For future phantom experiments a comparison of our results to radiographs taken at a conventional mammographic unit and to phase-contrast projections from a polychromatic X-ray tube setup would be desirable. Furthermore a reduction in dose and scan time could be achieved through an improvement of grating quality (higher visibility and thinning of wafers), optimized experimental procedure and advanced data processing. The results indicate a potential of improved tumor detectability in mammography screening programs.

In real breast tissue tumors are rarely as nicely isolated from the background as they are in the phantom studied in this section. The background that results from glandular tissue overlap can hinder a clear depiction of tumors in the breast (compare Fig. 8.1 (b)). To address this issue, follow-up mammography and tomosynthesis experiments on fixated breast tissue recorded at the CLS are presented in section 8.4. Corresponding benchmark images of the same sample obtained at a synchrotron beamline (ID19, ESRF) are presented in the following section 8.3.
8.3. Tomosynthesis: Synchrotron benchmark results

Mammography is currently the standard tool used in breast cancer screening. The technique is the first choice for the depiction of microcalcifications, which are an early indication of tumors, still it delivers unsatisfactory results in dense breasts. Due to glandular tissue overlap in dense breasts, tumor margins might be obscured or false positive caused by summation artifacts (O’Connell et al., 2010). Attenuation-based tomosynthesis has proven to successfully resolve tissue overlap but the technique’s ability to differentiate tumorous and glandular tissue is limited due to the small differences in X-ray attenuation in breast tissue. To overcome this limitation we investigate grating-based phase-contrast tomosynthesis and present first benchmark results of a breast specimen scanned at a synchrotron X-ray source. This phase-contrast tomosynthesis results clearly demonstrate a gain in diagnostically relevant information due to the ability of phase-contrast tomosynthesis to resolve tissue overlap in the breast and an improvement in tissue discrimination in the phase-contrast and dark-field tomosynthesis reconstruction as compared to conventional attenuation tomosynthesis. Results presented in this section have been submitted by Schleede et al. (2013)

The section is structured as follows: in section 8.3.1 the preparation of the breast sample as well as details on histopathological workup are presented; followed by a description of data acquisition and processing in section 8.3.2. In section 8.3.3 results from attenuation, phase and dark-field tomosynthesis are compared to one another as well as to registered histological sections. The section concludes with a summary and discussion in 8.3.4. Benchmark results presented in this section are compared to dose compatible results obtained from the CLS in section 8.4.

8.3.1. Sample preparation and histology

The study was conducted in accordance with the Declaration of Helsinki, was approved by the local ethics committee and written informed patient consent was obtained. We analyzed a mastectomy specimen from a 66-year-old woman containing an invasive ductal cancer. One representative sagittally orientated, 9 mm thick slice was chosen for tomosynthesis examination and fixed in 4% neutral-buffered formaldehyde solution (photograph of the sample, see Fig. 8.5 A). After image acquisition had been completed the breast slice was manually cut into 4 pieces of comparable size, suitable for further post-processing. Since the tissue sections exceeded the size used for standard staining procedures, they were manually enwrapped in a blotting paper for further processing and staining. All slices were dehydrated in an ascending alcohol series before embedding in hot paraffin wax. After solidification, the paraffin blocks were cut into 5µm sections using a standard microtome and sections were stained with hematoxylin and eosin using standard protocols. Imaging results are compared to histological sections in Fig. 8.9.

8.3.2. Data acquisition and reconstruction

The grating-interferometer setup at ESRF beamline ID19 comprises two X-ray optical gratings and a detector (Weitkamp et al., 2011). A silicon π-phase shift grating with
4.8 µm pitch (design energy 23 keV, fabricated at Laboratory for Micro- and Nanotechnology, Paul Scherrer Institut, Villingen, Switzerland) and a gold absorption grating with 2.4 µm pitch (gold thickness 74 µm, fabricated at Institute for Microstructure Technology and Karlsruhe Nano Micro Facility, Karlsruhe Institute of Technology, Germany) were used at the ninth fractional Talbot distance, corresponding to an inter-grating distance of 481 mm. A double-crystal monochromator selects X-rays of the desired energy and approximately $10^{-4}$ bandwidth from the wiggler spectrum. The grating interferometer is placed at 150 m distance from the wiggler source. The mean visibility was 54%. The tomosynthesis dataset consists of 61 equally spaced projections where the breast sample was rotated from $-30^\circ$ to $+30^\circ$. Twelve projections each comprising a field of view of (373 x 1376 pixel$^2$ corresponding to 12 mm x 41 mm) were recorded to cover the entire breast sample. Each projection consists of a phase-stepping scan of the phase grating with respect to the absorption grating, over one grating period using four steps. The exposure time for each phase step was 0.1 s when the sample was inserted and 0.05 s for the flat-field projections to avoid detector saturation. All images were recorded using a FReLoN CCD camera E2V-SN42 with a 125 µm thick LuAG:Ce scintillator (Crytur, Czech Republic) and nominal 30 µm pixel size. Dark frames were collected prior to the tomosynthesis scans. All raw phase stepping detector frames were dark current corrected. Subsequently, we used Fourier analysis to extract relative transmission, differential phase-contrast (DPC) and dark-field image (Pfeiffer et al., 2006). Twelve projections were stitched together to cover the entire sample by using a linear ramp function in the overlapping regions. Phase-contrast projections were further corrected by fitting a linear phase ramp. We used a filtered-backprojection algorithm (FBP) for the reconstruction from sinograms, which comprised 61 projection angles. A Ram-Lak filter was used to reconstruct attenuation and dark-field data and a Hilbert filter in the case of phase-contrast tomosynthesis (Pfeiffer et al., 2007b). To find a cutting plane in the 3D tomosynthesis volume that matches the histological sections shown in Fig. 8.9 (A-D) manual alignment was performed using the 3D visualization software VGStudio MAX.

### 8.3.3. Results

Fig. 8.5 shows projection images of the breast sample in all three modalities indicating a complementarity in information. Regions that appear homogeneous in the transmission image show various substructures in both the differential phase-contrast and the dark-field projections. In Fig. 8.6 three orthogonal views through the reconstructed phase-contrast tomosynthesis volume comprising 400 x 1683 x 2543 voxel are displayed, where strong artifacts stemming from the sparse angular sampling are observed. A central in-plane slice of the reconstructed 3D volume is presented in Fig. 8.7. The complementarity seen in the projection images is also evident here. A comparison of the zoomed regions (dotted red rectangles Fig. 8.7) shows that many tissue features are only visible in the phase and dark-field images. Furthermore, the contrast in the phase reconstruction appears to be less compromised by noise as compared to the attenuation image. This is in accordance with literature where small pixel sizes—as used in our experiment and in clinical breast imaging—are discussed as being advantageous in grating-based phase-contrast CT (Koehler et al., 2011). A zoom of the in-plane reconstructed phase-contrast
Figure 8.5.: Photograph of the 9 mm thick breast mastectomy slice (A). Projection images of the breast sample resulting from twelve frames that were stitched together to cover the entire sample. In the transmission image, glandular tissue (bright structures) containing a widespread carcinoma and fatty tissue (darker structures) are discriminated nicely (B). Regions that appear homogeneous in the attenuation image show substructures in the differential phase and the dark-field images. One example are fibrous structures, which appear more clearly in the differential phase-contrast projection (C) and in the dark-field image (D). The scale bar corresponds to 5 mm.
Figure 8.6.: Three views through the reconstructed phase-contrast tomosynthesis volume comprising 400 x 1683 x 2543 voxel. Red lines indicate respective cutting planes (images have been cropped to sample size).

Figure 8.7.: Central slice of the reconstructed tomosynthesis dataset of the breast showing: (A) conventional attenuation signal, (B) phase-contrast signal, and dark-field signal (C). Dotted rectangles in the images indicate two regions that are shown in magnified views in all three modalities. The images are scaled to provide maximum detail visibility (the scale bar corresponds to 5 mm).
Figure 8.8.: DPC projection of the breast showing a 28.5 mm × 20.7 mm (A). Images (B)-(F) display different phase-contrast tomosynthesis slices of the corresponding section of the sample with 2 mm separation each. Structures that are superimposed in the DPC projection (A) can clearly be attributed to a certain tomosynthesis slice. Fibrous structures visible in the lower right part of the DPC projection (red arrow) are only depicted in tomosynthesis slice (D) and (E). A parenchymal necrosis (green arrow, histological comparison in Fig. 8.9) is only depicted in slice (E) and not visible in the DPC projection image (A) (the scale bar corresponds to 5 mm).

Slices is with an in depth separation of 2 mm is shown in Fig. 8.8 B-F. In a comparison to the differential phase projection (Fig. 8.8 A) with reconstructed tomosynthesis slices the information gain becomes obvious. While going through the slices different features of the sample come in and out of focus. The marked parenchymal necrosis (green arrow) is visible most prominently in Fig. 8.8 E, whereas in the other reconstructed slices, structures below and above the parenchymal necrosis are in focus. Furthermore the fiber structures seen in the differential phase projection 8.8 A (red arrow) can clearly be localized within a limited depth in the sample. Attenuation, phase and dark-field tomosynthesis datasets were manually reoriented using the 3D visualization software VGStudio MAX to best match the histological sections shown in Fig. 8.9. The following prominent histological features (see Fig. 8.9 C,D) can be clearly differentiated in phase contrast and dark-field but not as well in attenuation contrast: dermal fibrosis (1), parenchymal necrosis (2), a region containing tumorous tissue (3) and necrotic tissue with an adjacent tumor spread (4). Especially feature (2), a parenchymal necrosis, is not visible in the attenuation tomosynthesis dataset due to the limited difference in soft-tissue attenuation. A contrast-to-noise analysis of the visibility of feature (1) and (2) in attenuation and phase-contrast is presented and compared to low dose results from the CLS in section 8.4.2 (table 8.2).
Figure 8.9.: Histological section zoom on a nodular necrosis with adjacent tumor extension (A). Zoom on dermal fibrosis (B). Histological section showing a parenchymal necrosis (2) a region containing tumorous tissue (3) and necrotic tissue with an adjacent tumor extension (4) (C). Histological section showing dermal fibrosis (1) (D). Cut through the 3D reconstructed volume that has been manually aligned to best match the histological slice showing attenuation (E), phase-contrast (F) and dark-field result (G). All features (1-4) are more clearly depicted in the phase-contrast and the dark-field tomosynthesis.
8.3.4. Summary and Discussion

In this section we presented the results of a grating-based phase-contrast tomosynthesis measurements of a human mastectomy sample section recorded at a synchrotron facility. Our results indicate superior diagnostic value due to the depth resolution supplied in tomosynthesis imaging: a region of necrotic tissue that is obscured in the projection image can clearly be depicted in one single tomosynthesis slice and fibrous structures visible in the differential phase-contrast projection can be attributed to a certain depth location in the sample.

Discerning tissue superposition artifacts from pathological structures is one of the challenges in diagnostic mammography. Phase-contrast tomosynthesis combines the advantage of improved soft-tissue discrimination in phase-contrast imaging with the ability of tomosynthesis to provide a third dimension so that the effect of improved visibility is not hampered by superposition artifacts. A comparison of conventional attenuation with phase-contrast and dark-field tomosynthesis demonstrates the complementarity of all three signals and an increase in diagnostic value is illustrated by using corresponding histological sections as a reference.

For supplying depth resolution in phase-contrast breast imaging we focused on tomosynthesis rather than breast CT as attenuation-based tomosynthesis is already successfully applied in both research studies and diagnostic clinical breast imaging. The reconstructed tomosynthesis views of the breast and the in-plane resolution are comparable to mammography views.

In this first proof-of-principle study we chose the well-established filtered-backprojection algorithm (FBP) to reconstruct the tomosynthesis dataset. There certainly is room for improvement of our reconstruction results either by using dedicated tomosynthesis filter designs or iterative reconstruction techniques as the benefit of both methods is well-established in conventional attenuation-based tomosynthesis (Dobbins, 2009). With respect to the noisy appearance of the attenuation tomosynthesis results we would like to point out that there exist dedicated post-processing algorithms to improve attenuation-based mammography images. We did not apply any post-processing in this study and we expect that attenuation as well as phase-contrast and dark-field image quality would improve significantly.

The setup and procedure of this benchmark synchrotron-based experiment was not optimized with respect to dose applied to the sample. The total dose was not prospectively evaluated, however the estimated dose is significantly higher than the dose applied in clinical mammography. Nevertheless the phase interaction of X-rays with matter exceeds the attenuation-based contrast by several orders of magnitude, which theoretically enables phase-contrast measurements at lower dose compared to conventional mammography. First dose compatible results in phase-contrast breast imaging support this assumption (Zhao et al., 2012; Schleede et al., 2012a). Further investigations thus focus on a translation of phase-contrast tomosynthesis to conventional X-ray tubes and the optimization of experimental setup, data processing and reconstruction routines to achieve clinically compatible exposure times. Dose compatible phase-contrast tomosynthesis measurements from the CLS, which are presented in the following section, constitute one step further towards a clinical implementation of the technique.
8.4. Tomosynthesis: CLS results

Following benchmark synchrotron results presented in section 8.3, we show low dose phase-contrast tomosynthesis images that were recorded at the CLS. The same mastectomy sample was measured at an X-ray energy of 21 keV to ensure comparable results. Despite significantly reduced image statistics and lower spatial resolution, prominent features visible in high dose benchmark measurements are preserved in the low dose case.

This section is structured as follows: in 8.4.1 the experimental parameters, data processing and reconstruction algorithms are presented. In the results section 8.4.2, we show multimodal projections and tomosynthesis slices at different depths in the sample. These results can directly be compared to the synchrotron benchmark results from the previous section. Image contrast in attenuation and phase tomosynthesis of both datasets is assessed quantitatively with contrast-to-noise ratio analysis in selected regions of interest. The section concludes with a summary and discussion of the tomosynthesis results obtained at the CLS.

8.4.1. Data acquisition and reconstruction

The mastectomy sample was measured at a mean X-ray energy of 21 keV with the Pilatus detector. For setup parameters please refer to table 4.1. A mean visibility of 40% was calculated from a flat-field image. In order to cover the entire sample, projections from eight sample positions were combined. Each projection comprises a stepping series with five images and an exposure time of 4 s. At each sample position a total of 31 tomosynthesis projections covering \( \pm 30^\circ \) was recorded. After every second sample position a series of 15 flat-fields was recorded. Fourier processing was used to calculate transmission, differential phase and a dark-field image. Eight sample positions were stitched together using linear ramps in the overlapping regions and an additional linear ramp that was subtracted from differential phase projections. The stitched projections cover a total of 372 pixel x 856 pixel. We used a filtered-backprojection algorithm (FBP) for the reconstruction of the sinograms, which comprised 31 projections. A Ram-Lak filter was used to reconstruct attenuation and dark-field data and a Hilbert filter was used in the case of phase-contrast tomosynthesis (Pfeiffer et al., 2007b).

A mean glandular dose of 39.36 mGy was calculated for the entire tomosynthesis scan. We used equations 8.2 and 8.3 considering the thickness of the breast slice of 9 mm without an outer skin layer (\( t_s = 0 \text{ cm} \)) and assuming a 50% glandular and 50% adipose by weight breast tissue composition. The mean glandular dose is a factor of 10 larger than the dose applied in conventional mammography. We consider the results as being dose compatible as we expect that thinning of the grating wafers, the use of a more efficient detector, matching X-ray energy and grating design energy lead to a significantly reduced dose within the 3 mGy limit for two view mammography (NCRP, 2004). Furthermore, the use of iterative reconstruction algorithms optimized for tomosynthesis application is expected to yield improved image quality and reduced dose applied to the sample.
8.4.2. Results

Multimodal images corresponding to the tomosynthesis projection at 0° are displayed in Fig. 8.10. Regions that appear homogeneous in the transmission projection exhibit substructures only visible in the differential phase and the dark-field projection. Due to significantly lower statistics as compared to the synchrotron benchmark projections in Fig. 8.5 the CLS projection images appear more noisy. Nevertheless, a strong phase and dark-field signal from the breast sample can be observed in the projections. Leftover fringes most prominent at the stitching borders of the differential phase and dark-field image arise from instabilities during the experiment and can potentially be reduced through the use of advanced processing schemes.

A central slice of the reconstructed tomosynthesis volume is shown in Fig. 8.11. Conventional attenuation, phase-contrast and dark field results are presented together with a zoom indicated by a red rectangle. Fibrous structures present in the phase-contrast zoom are not visible in the conventional attenuation signal. The attenuation result mainly shows two gray values representing fatty and glandular tissue, whereas the phase-contrast reconstruction shows strong gray value variations within the glandular regions of the breast, which also contains the tumor.

It should be noted here that we used cubic voxels both in the benchmark results and in the CLS case. Noise in the reconstructed images can be significantly reduced if an average over several in-depth slices is calculated. This is standard in clinical tomosynthesis imaging, where slices of 1 mm thickness are used to produce acceptable image quality at clinically compatible dose (Dobbins, 2009).

In analogy to Fig. 8.8 a comparison of a differential phase projection to different slices of reconstructed tomosynthesis data from the CLS is presented in Fig. 8.12. As discussed in the previous section the benefit of the 3D technique—tomosynthesis—lies in the ability to resolve structures that are projected on top of each other in (A) and to allow for a clear attribution of a certain feature to a designated position in the breast, which is important information for potential follow up biopsy exams. In order to quantitatively assess the benefit from phase-contrast tomosynthesis images as compared to conventional attenuation-based tomosynthesis, we performed contrast-to-noise analysis both on the benchmark dataset and on the CLS data. We selected a tomosynthesis slice where certain features had already been correlated to histopathology in Fig. 8.9. A corresponding slice was selected from the CLS dataset and a comparison of both images is presented in Fig. 8.13. Green rectangles indicate regions of interests (ROIs) that were used to calculate mean tissue gray values, \( M_1 \) and \( M_2 \), as well as one region outside the sample in the formalin filled volume, which was used to estimate the noise level \( \sigma_{bg} \). CNR values were calculated according to Tapfer et al. (2013):

\[
CNR = \frac{M_1 - M_2}{\sigma_{bg}},
\]

and are summarized in table 8.2. A CNR value above one designates a feature that is visible in an image, whereas \( CNR < 1 \) corresponds to features that are lost in the noise background of the image. From a comparison of the CNR values it is obvious that by using phase-contrast all features can be depicted more clearly compared to attenuation contrast. This applies both to the benchmark experiment and to the low dose case.
Figure 8.10.: Projection images of the breast sample resulting from 8 frames that were stitched together to cover the entire sample. In the transmission image, glandular tissue (bright structures) containing a widespread carcinoma and fatty tissue (darker structures) are discriminated nicely. Regions that appear homogeneous in the attenuation image show substructures in the differential phase and the dark-field images. One example are fibrous structures, which appear more clearly in the differential phase-contrast projection and in the dark-field image. The scale bar corresponds to 1 cm.
Figure 8.11.: Central slice of the reconstructed tomosynthesis dataset of the breast showing: (A) conventional attenuation signal (B) phase-contrast signal and dark-field signal (C). The dotted rectangle indicates a region that is shown in magnified views in all three modalities. The images are scaled to provide maximum detail visibility (the scale bar corresponds to 1 cm).
8.4. Tomosynthesis: CLS results

Figure 8.12: DPC projection of the breast showing a 37 mm×29 mm zoom (A). Images (B)-(F) display different phase-contrast tomosynthesis slices of the corresponding section of the sample with 2 mm separation each. Structures that are superimposed in the DPC projection (A) can clearly be attributed to a certain tomosynthesis slice. Fibrous structures visible in the lower right part of the DPC projection (red arrow) are only depicted in tomosynthesis slice (D) and (E). A parenchymal necrosis (green arrow, histological comparison in Fig. 8.9) is only depicted in slice (E) and not visible in the DPC projection image (A).
Figure 8.13: Comparison of benchmark synchrotron phase-contrast tomosynthesis data (A) to dose compatible results recorded at the CLS (B). Green rectangles are used for CNR analysis and are placed in regions containing dermal fibrosis, fat and parenchymal necrosis (for histological validation compare to figure 8.9). The rectangle covers 0.81 mm$^2$ and 3 mm$^2$ in (A) and (B) respectively.

<table>
<thead>
<tr>
<th>setup</th>
<th>tissue combination</th>
<th>$CNR_{att}$</th>
<th>$CNR_{pc}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRF</td>
<td>fat - necrosis</td>
<td>5.2 ± 0.2</td>
<td>74 ± 3</td>
</tr>
<tr>
<td>ESRF</td>
<td>fat - fibrosis</td>
<td>5.4 ± 0.1</td>
<td>133 ± 3</td>
</tr>
<tr>
<td>ESRF</td>
<td>fibrosis - necrosis</td>
<td>0.209 ± 0.005</td>
<td>60 ± 1</td>
</tr>
<tr>
<td>CLS</td>
<td>fat - necrosis</td>
<td>9.6 ± 0.7</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>CLS</td>
<td>fat - fibrosis</td>
<td>10.0 ± 0.7</td>
<td>18 ± 1</td>
</tr>
<tr>
<td>CLS</td>
<td>fibrosis - necrosis</td>
<td>0.43 ± 0.03</td>
<td>4.9 ± 0.3</td>
</tr>
</tbody>
</table>

Table 8.2: $CNR$ values calculated for ROIs in Fig. 8.13 and different tissue combinations. $CNR_{att}$ and $CNR_{pc}$ denote CNR value in the attenuation and in the phase-contrast reconstruction respectively.

The parenchymal necrosis with respect to fibrous tissue has a CNR value below one in attenuation tomosynthesis. This feature can thus only be resolved in phase-contrast tomosynthesis measurements. The benefit from using the phase image is not as large in the low dose case as compared to the synchrotron benchmark experiment. Besides the larger pixel size used in the low dose case, which favors attenuation instead of phase imaging, we would like to note that the CLS setup was not as optimized in terms of stability and grating quality as the grating interferometer at ID19. Nevertheless, all CNR values in the low dose case are well above 1 indicating that important features from the high dose measurement are preserved in the low dose case. Furthermore, we would like to point out that due to the difference in spatial resolution and experimental setup used, CNR values from the CLS and the ESRF are not directly comparable.
8.4.3. Summary and Conclusion

In summary we showed the first tomosynthesis results recorded at the CLS, where a mastectomy specimen was scanned at a clinically compatible X-ray energy of 21 keV. In the projection images as well as in the reconstructed slices superior diagnostic information is obtained through the combination of enhanced soft-tissue contrast obtainable from the phase image and from the depth resolution supplied in tomosynthesis. Features that are visible in the benchmark synchrotron experiment are preserved in the dose compatible data obtained from the CLS. Improved soft-tissue contrast in the phase images as compared to attenuation tomosynthesis alone, was demonstrated visually and quantitatively in a CNR analysis.

8.5. Summary: Advances in breast imaging

To conclude, I would like to come back to the two main issues in clinical breast imaging with X-rays that were introduced in the beginning of this chapter: (1) low soft-tissue contrast in conventional attenuation images; (2) overlapping structures that obscure tumors or mimic tumors structures in projection images of the breast. Improved soft-tissue contrast was demonstrated in a mammography phantom study presented in the first part of this chapter. Complementary information from differential phase and scattering information from dark-field projections proved beneficial in the detection of tumorous masses and fibrous structures. To address the problem of overlapping structures present in real breast tissue we investigated phase-contrast tomosynthesis of a mastectomy sample recorded both at a large-scale synchrotron and at the CLS. Benchmark results from the synchrotron demonstrated improved soft-tissue contrast in the phase images as well as additional diagnostically relevant information obtained from the depth resolution in tomosynthesis data. Features better resolved in the phase-contrast tomosynthesis comprised fibrous structures and necrotic tissue. In a dose compatible tomosynthesis measurement at the CLS we could show visually and quantitatively that these features are preserved in the low dose images. Our results indicate a potential benefit of using phase-contrast tomosynthesis in clinical breast imaging. Future steps towards this goal include a translation to conventional X-ray tube sources, improvements in data processing, e.g. iterative reconstruction schemes optimized for differential phase-contrast tomosynthesis, a reduction in overall scan time towards clinically tolerable values as well as a study including whole breast samples and different types and grades of breast cancer.
9. Propagation-based CT at a laser-plasma source

In this chapter we present the first phase-contrast micro-tomogram of a biological sample from a fully laser-driven betatron X-ray source, along with a comprehensive source characterization. Presented results are based on a manuscript, which has been submitted by Wenz et al. (2013).

This chapter starts with a short motivation in section 9.1, followed by a description of the betatron source and the imaging setup in section 9.2. In section 9.4 we present details on data acquisition and treatment of the raw images. As a basis for quantitative reconstruction of the tomogram presented in section 9.5, we performed a careful characterization of the X-ray source in terms of its transverse coherence and spectrum, which is described in section 9.3. The chapter concludes with a summary of the obtained results in section 9.6.

9.1. Motivation

Propagation-based phase-contrast imaging has proven to yield quantitative high resolution CT results useful in a variety of applications in material research and biomedical imaging (Gureyev et al., 2009). The necessary high spatial coherence is currently provided by either large-scale synchrotron facilities (Cloetens et al., 1999) with limited beamtime access or by microfocus X-ray tubes (Wilkins et al., 1996) with rather limited flux.

X-rays radiated from betatron oscillations in a laser-driven plasma can be employed as an alternative. These sources offer the required high spatial coherence and have the potential for high flux at low X-ray energies along with short X-ray pulses on the order of fs, which can be used for pump-and-probe experiments. Here we present a phase-contrast micro-tomogram revealing quantitative electron density values of a biological sample, which reflects the stability level that is achievable with laser-driven betatron sources.

9.2. Laser-plasma betatron source

The following experiments were performed using the ATLAS Ti:Sapphire laser at the MPI for Quantum Optics. It occupies a table area of approximately 5 m, and delivers 1.6 J-energy, 28 fs-duration (57 TW) laser pulses, centered at 800 nm wavelength. They are focused onto the entrance of a Hydrogen-filled gas cell (see Fig. 9.1) by an off-axis parabolic mirror (f=1.5 m, F/20) to a spot size of 22 µm FWHM. This corresponds to
Figure 9.1.: The laser pulse (1.6 J, 28 fs, 57 TW) (red) is focused by a F/16 off-axis parabola to a 22 µm diameter spot size on the entrance of a 6 mm long gas cell with a plasma electron density of \( n_p = 1.1 \times 10^{19} \text{ cm}^{-3} \). The residual laser light is blocked by two 10 µm thick Aluminum foils. Dipole magnets deflect the accelerated electrons (yellow) away from the laser axis onto a scintillating screen (LANEX). The X-ray beam (pink) transmitted through the foil is recorded by a cooled back-illuminated X-ray CCD with 22.5 µm square pixels. The tomogram was acquired in the experimental configuration as shown, the Al-cake and wire-arrangement can be inserted into the X-ray beam for spectral and source size characterization.
a vacuum peak intensity of $2 \times 10^{19}$ W cm$^{-2}$. At these intensities, the hydrogen is fully ionized and the laser propagates through a plasma. The wave phase velocity matches the laser group velocity, so that in the frame of the laser pulse, the plasma wave constitutes a co-moving accelerating field. Electrons from the plasma are trapped into this wave by wavebreaking and accelerated to relativistic energies around 200-400 MeV, in a process known as laser-wakefield acceleration (LWFA).

A magnet deflects the electron beam according to energy onto a scintillating screen (see Fig. 9.1). From the position and brightness on the screen the energy, divergence and charge of the electron bunch can be deduced (Buck et al., 2010). For our pulse parameters the highest electron energies with a peak at 400 MeV, lowest divergences (1.3±0.3 mrad FWHM) and moderate charges (50 pC) were produced at plasma electron densities of $5 \times 10^{18}$ cm$^{-3}$, created from laser-induced field ionization of the target gas.

The betatron motion leads to the emission of well-collimated X-ray beams with a critical energy of 4.8 keV, measured by their transmission through a stack of filters (Sidky et al., 2005). However, when the plasma density is increased to $1.1 \times 10^{19}$ cm$^{-3}$, the electron energy drops to 200 MeV and the divergence increases to 10 mrad, along with a substantial increase of electron beam charge to 400 pC. Now the X-ray beam divergence triples from 5 mrad to 15 mrad and the photon fluence increases ten-fold, while the energy spectrum stays roughly constant (see Fig. 9.2). This results from the dramatic increase of both trapping efficiency and radial field strength of the plasma wave at higher densities. Now the electrons wiggle in stronger fields, which together with the fixed lower-energy cutoff due to the light-blocking filters (see Fig. 9.1) leads to a similar emission spectrum. More trapped electrons and higher fields contribute to the signal increase. This betatron-optimized regime results in the emission of $10^8$ photons/shot above 2 keV.

For our experimental conditions, even a small off-axis distance of 1 µm corresponds to a wiggler parameter on the order of 10, leading to high harmonic orders. For the spectrum measurement, the X-rays are freely propagating from the source to an Andor model DO432 BN-DD back-illuminated CCD detector at a distance of 3.26 m. The on-axis laser light is blocked behind the source by two 10 µm thick Al-foils. For the source-size and tomography studies the sample is mounted $l = 0.73$ m from the source, $D = 1.99$ m in front of the detector, yielding a 3.7x magnification. A filter cake for spectral characterization by absorption in different material thicknesses and a Tungsten wire for source size characterization can be moved into the beam.

### 9.3. X-ray spectrum and source size reconstruction

**Spectrum reconstruction**

X-ray spectra as seen by the sample were reconstructed from transmission measurements through an aluminum filter cake (see inset in Fig 9.2 (a)) by using an algorithm introduced by Sidky et al. (2005). Despite the known absorption properties of the aluminum filters at the respective energies in the spectrum the algorithm uses the response function of the detector as an input. The filter cake comprises aluminum of thicknesses ranging from 20-630 µm. X-ray spectra reconstructed from 17 laser shots as well as an average spectrum are shown in Fig. 9.2 (a). In accordance with theory (compare section 2.4.4)
9.3. X-ray spectrum and source size reconstruction

Figure 9.2.: (a) X-ray spectra as seen by the sample for 17 laser shots, reconstructed from the transmission through an aluminum filter cake (inset) with overall thicknesses ranging from 20-630 µm. Average spectrum (red solid line), standard deviation (blue solid lines), and bending magnet spectrum (black dashed line) (b) Measured intensity distribution integrated along the curvature of a 100 µm thick tungsten wire (inset) and the modeled intensity distribution for a Gaussian spot size and the retrieved spectra of (b) revealing an upper limit on the source size of 2.0 µm rms.

the obtained spectra can be fitted to the shape of a bending magnet (or wiggler) spectrum (equation 2.8) with a critical energy of 2.2 keV.

Source size determination
The source size was derived by analyzing the Fresnel diffraction pattern from a tungsten wire backlit by the X-ray beam. The measured edge diffraction on the detector from a 100 µm thick Tungsten wire (26 cm behind the source) is shown in the inset of Fig. 9.2 (b), and was compared to modeled distributions for various source sizes. They were obtained by summing up the Fresnel diffraction from a knife edge, as described in e.g. Born and Wolf (1998) for all energy bins of the incident spectrum weighted by the CCD response. The beam, showing a Gaussian shape on the CCD chip, was assumed to be Gaussian at the origin. The resulting curves for different source sizes are shown in Figure 9.2 (b). In order to improve the signal to noise ratio, we have vertically summed up the profiles, taking into account the curvature of the wire by a cross-correlation between different rows. Our analysis yields a best fit for a source size of 2.0 ± 0.2 µm FWHM.

Assuming pulse durations of 5 fs as suggested by numerical studies and recent reports by Buck et al. (2011); Lundh et al. (2011), the source exhibits a peak brilliance of $5 \times 10^{22}$ photons s$^{-1}$ mm$^{-2}$ mrad$^{-2}$ per 0.1% bandwidth. In the current proof-of-principle experiment, the average brilliance and photon flux density at the sample was limited to $2.5 \times 10^7$ photons s$^{-1}$ mm$^{-2}$ mrad$^{-2}$ per 0.1% bandwidth and $10^7$ photons s$^{-1}$ cm$^{-2}$, respectively, corresponding to a shot rate of 0.1 Hz due to gas load in the chamber and data acquisition limitations. With an optimized pumping design and improved 5 Hz
data acquisition, allowing to use the full repetition rate of our laser system, these figures could be improved by a factor of 50, yielding few-minute scan times. The scalability of the photon energy depends on the electron energy, the plasma density and the wiggler strength parameter, which in LWFA are all interlinked (Esarey et al., 2009). Clever target engineering, i.e. separating acceleration and radiation zone, off-axis injection (Popp et al., 2010) or laser-betatron resonance effects (Cipiccia et al., 2011) may strongly enhance the betatron amplitude and hence the critical energy. In Cipiccia et al. (2011), a 20-keV X-ray spectrum with a tail to 1 MeV was achieved with a laser only three times more energetic than ours. The shot-to-shot stability of our X-ray source is excellent for a laser-driven process, yielding an X-ray beam in > 95% of all laser shots, with low fluctuations of the X-ray spectrum (see Fig. 9.2 (a)), and a photon number constant to within ±30%, making it suitable for multi-exposure tomography.

9.4. Data acquisition and processing

We measured a dried insect (Chrysoperia carnea, green lacewing, photograph see Fig. 9.5) with propagation-based phase contrast at a single propagation distance. 1487 single-shot phase-contrast images taken from various angles were recorded. Raw images feature a field of view of 7.5×6.9 mm² and a resolution of 6 µm.

For the tomography scan, the insect was placed on a rotating mount into the X-ray beam (see Fig.9.1) and raw phase-contrast images were recorded on the CCD. In order to correct for the fluctuations of the X-ray source position caused by shot-to-shot laser pointing fluctuations, four images at each projection angle were registered using normalized cross correlation. The shape of the correlation surface is assumed to fit two orthogonal parabolic curves. Sub-pixel registration accuracy is obtained by fitting a paraboloid to the 3×3 pixel vicinity of the maximum value of the cross correlation matrix. Sub-pixel shifting is performed in Fourier space. To account for the Gaussian intensity profile of the X-ray beam, the sample is masked out using an edge detection filter and images are background corrected by subtracting a second order polynomial.

Raw projection images exhibit the so-called edge-enhancement effect (see insect’s wings and hair in Fig. 9.3 (a)), which is inherent to propagation-based phase-contrast imaging (Cloetens et al., 1997) in the Fresnel-diffraction regime. No optical elements between the source and the detector are used, but the wave propagates sufficiently far beyond the sample (1.99 m) for Fresnel diffraction to occur. The edge-enhanced image is useful by itself for visual inspection when high-resolution features with poor absorption contrast (Fig. 9.3 (a)) are of particular interest. However, propagation-induced intensity fringes of a pure phase object are not a direct measure of the phase shift but rather the Laplacian of the phase front (Wilkins et al., 1996). A reconstruction of raw phase projections will thus only yield gray level variations at material interfaces (Fig. 9.4 (a)). Due to the missing link of reconstructed contrast to material properties, quantitative analysis and automatic segmentation via thresholding is not possible.
9.5. Phase retrieval and CT reconstruction

In absorption tomography, projections of the linear absorption coefficient along the beam are directly obtained from the logarithm of the recorded intensity. The subsequent reconstruction exhibits area contrast with gray values directly related to material properties of the sample under investigation. Starting from edge-enhanced projections, phase-retrieval algorithms are employed to create line-projection images of the refractive index decrement $\delta$.

We use a single-distance quantitative phase retrieval method that does not require the sample to show negligible absorption (Paganin et al., 2002). It employs a single material constraint corresponding to a fixed $\delta/\beta$-ratio representing the sample’s main chemical component. This assumption and a comparably weak absorption allows for a quantitative reconstruction of electron density values in the sample as shown in Myers et al. (2007). The projected thickness $T(\vec{r})$ of the sample, which is directly related to the phase shift imposed onto the wavefront via $\phi(\vec{r}) = -2\pi/\lambda_{\text{mean}} \delta_{\text{poly}} T(\vec{r})$, can be retrieved by using the following equation (Paganin et al., 2002):

$$T(\vec{r}) = -\frac{1}{\mu_{\text{poly}}} \ln \left( \mathcal{F}^{-1} \left\{ \mathcal{F} \left\{ M^2 I(M\vec{r}) \right\} / I_0 \right\} \right),$$

(9.1)
Figure 9.4.: (a) The reconstructed transverse slice of the lacewing without phase retrieval prior to reconstruction highlights material boundaries but does not allow for a quantitative analysis. (b) The same transversal slice reconstructed after phase retrieval. (c) Reconstructed transverse slices with gray values representing electron density values. The reconstruction exhibits good area contrast allowing for volume rendering and segmentation as shown in Fig. 9.5.

where \( T(\vec{r}) \) is the retrieved thickness of the sample, \( \vec{r} \) are the transverse coordinates, \( \vec{k} \) are the Fourier space coordinates, \( I \) is the measured intensity, \( I_0 \) is the uniform intensity of the incident radiation, \( M \) is the magnification of the image, \( D \) is the distance from the sample to the detector and \( \delta_{\text{poly}} \) and \( \mu_{\text{poly}} \) are the material dependent linear absorption coefficient and refractive index decrement, respectively.

In the case of a polychromatic X-ray spectrum accurate phase retrieval results are achieved through the calculation of effective \( \delta \) and \( \mu \) values. We assume the main chemical composition present in the dried insect to be Chitin \( \text{C}_8\text{H}_{13}\text{NO}_5 \). Values of \( \mu_{\text{poly}} = 52.41 \text{ cm}^{-1} \) and \( \delta_{\text{poly}} = 1.54 \times 10^{-5} \) were calculated from reconstructed X-ray spectra (see Fig. 9.2 (b)), tabulated \( \mu(E) \) and \( \delta(E) \) values at a density of \( \rho = 2.2 \text{ g cm}^{-3} \) (Gullikson), and the known detector response function (Mayo et al., 2003). The phase map as depicted in Fig. 9.3 (b) was reconstructed using equation 9.1 with values of \( D=199 \text{ cm} \), \( M=3.7 \) and a mean energy as seen by the detector of \( E_{\text{mean}} = 6.7 \text{ keV} \) (\( \lambda_{\text{mean}} = 1.85 \text{Å} \)). As the retrieved phase map is directly related to the integrated decrement \( \delta \) of the index of refraction, the reconstruction yields information on electron density distribution in the sample. Before reconstruction, the 360 projections taken over 360° were binned by a factor of two in both image dimensions to yield an artifact-free reconstruction. The vertical alignment of the tomography scan is performed using cross correlation of integrated pixel values perpendicular to the tomography axis. Horizontal alignment was performed manually. Standard filtered back projection (FBP) was used to reconstruct.
the transverse slices shown in 9.4 (b) and (c). The reconstruction reveals a distinct contrast between insect and background, allowing segmentation via simple thresholding. A 3D rendering of the sample is presented in Fig. 9.5, including sectioning planes of the 3D volume with gray levels corresponding to electron density.

9.6. Summary and Discussion

In this chapter we presented a propagation-based phase-contrast CT scan from a laser-driven Betatron source. Source characterization as well as phase retrieval techniques have been applied to yield a quantitative reconstruction of electron density values in the insect.

Our results demonstrate that fully laser-driven X-ray sources have reached the verge of practical usefulness for application-driven research. Especially in view of the ongoing dynamic evolution in high-energy, high-repetition rate laser technology (Metzger et al., 2009; Tümmler et al., 2009) aiming to scale multi-TW lasers to kHz and beyond, average fluences approaching current state-of-the art compact synchrotron sources are expected to become available in the future. Due to the short pulse lengths supplied, these sources allow for time-resolved imaging with femtosecond resolution on a laboratory scale.
10. Summary, conclusions and perspectives

This chapter summarizes the main scientific findings obtained within this PhD thesis. Results are evaluated and an outlook to ongoing developments and further research possibilities is given. This summary is structured according to the chapters 4 to 9.

Experimental setup development
With the installation of a scintillation counter at the CLS grating-interferometer setup, the intensity normalization of measurements with large samples is now possible. Furthermore, the counter allows for data acquisition gating in adaption to beam intensity fluctuations.

Regularized integration
An existing iterative algorithm for the regularized integration of differential phase-contrast projections was extended to allow for a zero-background constraint in the measurements of isolated samples. The algorithm was evaluated in the context of mammography, where a significant reduction of stripe artifacts compared to direct integration was achieved. The regularized integration of CT projections prior to reconstruction proved to reduce sagittal stripe artifacts, which are inherent to differential phase-contrast CT data.

The obtained results allow for a direct comparison of attenuation and phase-contrast mammography results, which is important as radiologists are not trained to interpret differential projection images. The possibility to retrieve the projected phase from differential phase projections allows for more flexibility in experimental setup design. This is due to the fact that the integration step is decoupled from the CT reconstruction and therefore enables arbitrary orientations of the grating interferometer with respect to the tomography axis.

The algorithm has to be tested with mammography measurements of larger samples such as full mastectomy specimens to access the potential clinical use. Additional regularization terms can be implemented to cope with strong phase signals such as phase wrapping at air-sample interfaces and to reduce low frequency artifacts.

Pulmonary emphysema imaging
The regional distribution of pulmonary emphysema is not accessible from conventional thorax radiographs. Grating-based imaging of excised mouse lungs at the CLS showed, that the dark-field signal can be used to visualize changes in lung microstructure. Furthermore, a combined visualization of attenuation and dark-field projection images was introduced, which allows to directly assess the regional distribution of emphysema from a single multimodal projection measurement.
Our results have triggered a series of experiments towards the translation to preclinical imaging. Measurements of excised samples at a small-animal CT scanner equipped with a grating interferometer and a conventional X-ray tube source demonstrated, that our approach is feasible with polychromatic sources (Yaroshenko et al., 2013). The scientific relevance of the obtained results is reflected in the fact that the first ever grating-based in-vivo studies, which are currently undertaken at our chair, aim at the assessment of pulmonary emphysema with dark-field imaging.

Future studies should investigate different stages of the disease and look into the accuracy of the proposed analysis, which is potentially compromised by overlying structures in the mouse such as ribs and fur. Furthermore, other common pulmonary diseases such as lung fibrosis and lung tumors should be investigated as they also exhibit significant changes in lung microstructure and could therefore benefit from a strong signature in dark-field projection images.

**Quantitative CT**
Absorption-based monochromatic CT measurements at the CLS demonstrated a significant reduction of beam hardening artifacts compared to polychromatic CT measurements with an X-ray tube setup. The quantitative accuracy of the absorption and phase-contrast CT results was verified in a fluid phantom study. Enhanced soft-tissue contrast was demonstrated in a small-animal ex-vivo phase-contrast CT measurement.

Low soft-tissue contrast is the main drawback of conventional absorption based CT and grating-based imaging could thus in a first step improve the study of small animal tumor models. The monochromatic beam can be exploited in quantitative absorption-based CT measurements of for example fossils or industrial samples.

**Breast imaging**
Conventional mammography faces two major challenges, namely limited soft-tissue contrast and overlapping glandular structures, which hinder tumor detection in breast projection measurements.

We demonstrated improved detectability, e.g. higher contrast-to-noise-ratios, of small tumor-like masses in a mammography phantom, when using phase-contrast and dark-field information, as compared to the attenuation signal alone. Measurements were carried out in a dose compatible setting at the CLS. Our results further indicate the need for the development of dedicated phase- and dark-field mammography phantoms as the currently available phantoms mainly mimic breast tissue with respect to its absorption properties.

To supply depth resolution, the first grating-based phase contrast tomosynthesis scan of a mastectomy sample slice was performed both in a synchrotron benchmark experiment and in a dose compatible experiment at the CLS. It was shown that additional diagnostically relevant information is obtained by the combination of enhanced soft-tissue contrast in phase-contrast imagines with the depth resolution supplied by tomosynthesis. We showed that commonly used FBP with a Hilbert filter is sufficient to reconstruct differential phase tomosynthesis data.

Future work should focus on the measurements of full mastectomy samples and the translation to more commonly available X-ray tube setups. Advanced reconstruction algorithms specific to limited angle phase-contrast tomosynthesis should be developed.
as these have shown to significantly improve image quality in absorption-based tomosynthesis.

**Proof-of-principle laser plasma betatron CT**
The first proof-of-principle propagation-based CT conducted at a laser plasma betatron X-ray source was analyzed and successfully reconstructed. Future work should focus on an optimization of propagation distances and data acquisition for PBI-CT. Furthermore up to now we have not exploited the unique short X-ray pulse lengths supplied by the source, which could be used in pump-and-probe experiments.

Overall, we believe that the adaption of experimental setups and advances in data processing obtained within this thesis work allow to exploit a broader range of samples with the grating interferometer at the CLS and elsewhere. The translation of synchrotron breast imaging benchmark results to dose compatible experiments at compact sources, as well as the identification of new clinical cases, which benefit from the use of multi-modal imaging approaches serve as further steps towards a clinical implementation of grating based phase-contrast imaging.


E. Gullikson. X-ray interactions with matter. 

T. E. Gureyev, S. C. Mayo, D. E. Myers, Y. Nesterets, D. M. Paganin, A. Pogany,


Bibliography


Publications and scientific presentations

In this chapter, all publications and scientific presentations (oral and poster) related to this thesis are listed chronologically. The list of publications is categorized into first-authored and co-authored publications.

First-authored publications (peer-reviewed)


Co-authored publications (peer-reviewed)


**Oral presentations**

Title: Phase-contrast imaging with Compact Light Source based on inverse Compton X-rays, *Frühjahrstagung der Deutschen Physikalischen Gesellschaft*, Dresden, Germany, March 2011.


**Poster presentations**

Title: First Experiments with a Laser-Driven Compact Synchrotron X-ray Source, *CIMST Summer School on Biomedical Imaging, ETH Zurich, Switzerland, September 2011.*


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