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Marie-Christine Zdora

X-ray Phase-Contrast Imaging Using Near-Field Speckles

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X-ray Phase-Contrast Imaging Using Near-Field Speckles

Doctoral Thesis accepted by
University College London, London,
United Kingdom

Springer

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ISSN 2190-5053 ISSN 2190-5061 (electronic)
Springer Theses
ISBN 978-3-030-66328-5 ISBN 978-3-030-66329-2 (eBook)
https://doi.org/10.1007/978-3-030-66329-2

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Supervisors' Foreword

The principle of phase-contrast imaging, exploiting the wave properties of light, was introduced for the visible-light regime in the 1930s by Frits Zernike. For the first time, phase shifts induced by the imaged object, which carry important information on the sample's properties, could be visualised in a microscopic image. Phase-contrast imaging revolutionised the field of visible-light microscopy and was recognised with the Nobel Prize in Physics in 1953. More than a decade later, the concept was translated to the X-ray regime by Ulrich Bonse and Michael Hart. They developed an X-ray crystal interferometer, today known as Bonse-Hart interferometer, to translate X-ray phase effects into intensity modulations recorded by a detector. As for visible light, the X-ray phase-contrast signal leads to significantly improved image contrast, in particular for samples with small density differences, which can hardly be visualised by the conventional absorption-based modality. At first not widely applied due to the limitations in the available instrumentation, X-ray phase-contrast imaging was further pursued in the 1990s with the advent of high-brilliance X-ray synchrotron sources and more advanced X-ray optics. A number of groups started working on X-ray phase-contrast imaging during this time and introduced various other X-ray phase-contrast imaging techniques, such as analyser-based imaging, propagation-based imaging, the edge-illumination approach and Talbot(-Lau) grating interferometry. X-ray phase-contrast imaging methods have since seen increasing interest in the last decade for a wide range of applications, one of the most promising being (bio-) medical imaging.

In recent years, efforts have increasingly been directed towards the development and simplification of X-ray phase-contrast methods, also focussing on their translation from synchrotron facilities to lower brilliance conventional laboratory X-ray sources. X-ray speckle-based imaging, introduced in 2012, is a simple yet very sensitive and quantitative method to measure the phase shift induced by the sample and can be adapted to conventional X-ray sources. The beauty of the technique lies in the use of a simple optical element, such as a piece of sandpaper, to modulate the X-ray wavefront and create interference effects, from which the phase information is extracted. The great interest of the X-ray imaging community in speckle-based imaging has resulted in its rapid development, to which Marie-Christine Zdora's Ph.D. project has contributed significantly. Her work is a multidisciplinary project spanning from theoretical advances and algorithmic developments to applications of the method to relevant research areas.

Marie-Christine Zdora put X-ray speckle-based imaging in context with another powerful X-ray phase-contrast method named grating interferometry and unified these two methods with an innovative algorithmic approach for phase extraction from interferometric data, the Unified Modulated Pattern Analysis, applicable also to other wavelengths. She subsequently focussed on demonstrating the potential of her method to various scientific applications, a range of which she presents in this thesis.

By exploiting the high accuracy and high precision of the phase shift measured with X-ray speckle-based imaging, Marie-Christine Zdora performed in-situ metrology of X-ray optics, such as refractive X-ray lenses, commonly used at synchrotron facilities. The results are relevant for the X-ray synchrotron community to accurately characterise the optical components of synchrotron beamlines.

When combined with tomography, X-ray speckle-based imaging allows for the visualisation of the inner structure of the sample and directly measures its mass density distribution. Marie-Christine Zdora used X-ray speckle-based tomography to answer relevant questions in materials science and geology, also extending the technique to higher X-ray energies to image denser and thicker samples.

Marie-Christine Zdora pioneered the development of X-ray speckle-based tomography for three-dimensional virtual histology of biomedical soft tissue (biopsies from human tissues and full organs of small animals) in near-native state. The data obtained in this way complement and advance the images from conventional histopathology, while preserving the real three-dimensional connectivity information and mapping in detail even the tiniest and most localised inhomogeneities in the sample.

Another crucial development was the translation of the Unified Modulated Pattern Analysis to conventional laboratory-based X-ray systems, making it accessible to a wider range of users.

When Marie-Christine Zdora was only 2 years into her Ph.D. project, she had already been recognised by the X-ray imaging community as a pioneer of speckle-based imaging. The impact of her Ph.D. work has been awarded by an important recognition in our field, the Werner Meyer-Ilse Award for excellence in X-ray microscopy in 2018. The expertise and deep understanding that Marie-Christine Zdora has demonstrated is also reflected in the first review article in X-ray speckle-based imaging that she has published as a single author during her Ph.D. project.

This thesis will serve as a handbook of X-ray speckle-based imaging, providing a comprehensive introduction to the technique and a guide on successfully implementing it at synchrotron beamlines and laboratory-based systems. The high quality and the diligent, detailed analysis of the experimental results presented in the following pages speak for themselves. This work will be highly valuable not only to the X-ray imaging community, but also disciplines that benefit from high-contrast imaging as well as accurate quantitative phase sensing and density measurements, such as metrology and optics characterisation, the biomedical and clinical fields, materials science, geology, palaeontology and archaeology, among others. We anticipate the uptake of X-ray speckle-based imaging in these fields in the near future.

Southampton, UK
September 2020

Dr. Irene Zanette
Prof. Pierre Thibault

Abstract

In the last decades, X-ray phase-contrast imaging has proven to be a powerful method for unveiling the inner structure of samples and is capable of visualising even minute density differences. Recently, speckle-based imaging (SBI), the youngest X-ray phase-sensitive technique, has received great interest due to its high sensitivity, quantitative character and relaxed requirements on the setup components and beam properties.

This thesis is focussed on the development, experimental optimisation and applications of SBI, with the aim of simplifying its implementation, increasing its flexibility and expanding its potential.

For this, a robust, flexible data acquisition and reconstruction approach, the unified modulated pattern analysis (UMPA), was developed, which lifts previous constraints of SBI. UMPA allows for tuning of the sensitivity and spatial resolution by adjusting the scan and reconstruction parameters. It is applicable not only to random speckle but also periodic interference patterns, bridging the gap and improving the performance of both speckle- and single-grating-based techniques.

Following the first demonstration of UMPA, its potential for a range of applications is illustrated in this thesis. It is shown that UMPA can be employed for X-ray optics characterisation to quantify aberrations in the focussing behaviour of X-ray refractive lenses with high precision and accuracy. UMPA phase tomography is applied to the field of biomedical imaging for high-sensitivity three-dimensional (3D) virtual histology of unstained, hydrated soft tissue, giving unprecedented structural and quantitative density information.

Further developments of SBI explored in this thesis include the testing of novel customisable speckle diffusers, the extension of SBI to higher X-ray energies for geology and materials science applications and the demonstration of UMPA at a laboratory X-ray source. These progresses promise new possibilities of SBI for high-sensitivity, robust and high-throughput imaging in previously inaccessible fields and make SBI accessible to a wider range of users in research and industry.

Acknowledgements

This Ph.D. project would not have been possible without the contributions and support of my supervisors, collaborators and colleagues. It has been a pleasure working with so many wonderful and bright people from whom I have gained a lot of knowledge and inspiration.

First and foremost, I would like to sincerely thank my main supervisors Irene Zanette and Pierre Thibault who have supported and guided me at all times throughout this project. I have learnt so much from you and I am very lucky to have had such knowledgeable and at the same time kind and caring supervisors. It was just wonderful to work with you and I hope we will continue to collaborate in the future! Thank you for always being available for support, answering my numerous questions and giving me the freedom to work on topics that interest me.

I would also like to thank my supervisor at Diamond Light Source, Christoph Rau, for giving me the opportunity to work at his beamline and providing me with plenty of resources throughout the last years, including financial support for several conference trips. I would, furthermore, like to acknowledge Diamond Light Source for funding my joint Ph.D. studentship with UCL.

Thanks to my secondary supervisor at UCL, Alessandro Olivo, who provided valuable feedback during the upgrade viva that was very helpful for the writing of this thesis. I am, furthermore, grateful to Desmond McMorrow for having been my second examiner for the transfer exam.

A special thanks goes to my former Ph.D. colleagues in Pierre's group at UCL: Simone Sala, Stephanos Chalkidis and Charan Kuppili. Thanks for sharing many beamtime and conference experiences—it was always great fun with you guys! I would also like to thank the former and current members of Pierre's group at Southampton, Hans Deyhle, Sharif Ahmed, Toby Walker and Ronan Smith, for their support during beamtimes at the synchrotron and in the lab.

I would like to acknowledge the whole group at Diamond I13 beamline, especially Kaz Wanelik and Malte Storm who helped with various problems and always had a kind word for me.

My gratitude goes to all my collaborators who I have had the pleasure to work with over the course of my Ph.D. project. Special thanks to the group at ID19 at the

ESRF, especially Alexander Rack and Margie Olbinado, for the many successful and interesting beamtimes and for supporting my work. I have learnt a lot at ID19! Thanks to the group of Bert Müller at the University of Basel for inviting me to many of their beamtimes, which taught me a lot about grating interferometry: Bert Müller, Georg Schulz, Anna Khimchenko, Griffin Rodgers, Christos Bikis and Peter Thalmann. Special thanks also to Willy Kuo, University of Zurich, who provided many of the biomedical samples and was always available to help and explain biological things to me. Thanks to the people at the Faculty of Medicine, University of Southampton, Peter Lackie, Orestis Katsamenis and Matthew Lawson, who helped substantially with the histology of the kidney sample. Thanks also to Vincent Fernandez, Natural History Museum London, for his help with the kidney project, in particular, his amazing VGStudio skills and his appreciation of Bavarian beer. Thanks to Joan Vila-Comamala for introducing me to I13 and for the collaborations and beamtime support on speckle imaging. Thanks to Frieder Koch and Arndt Last from KIT for the collaboration on lens characterisation and Jenny Romell from KTH Stockholm for beamtime support. Thanks to my collaborators at Diamond, Tunhe Zhou and Nghia Vo, for the great beamtimes at I13 and I12 on various topics (and lots of popcorn). Furthermore, thanks to Beverley Coldwell and Fei Yang for providing samples. I would like to thank also collaborators on several projects that were not directly related to my Ph.D. project, but nonetheless extremely interesting: Patrik Vagovič from DESY and XFEL, Irvin Teh and Jürgen Schneider from the School of Medicine, University of Leeds (previously University of Oxford), Roger Benson, Armin Schmitt and Donald Davesne from the Earth Sciences Department, University of Oxford, Carles Bosch Piñol and Andreas Schaefer from the Francis Crick Institute, London.

Moreover, I would like to express my gratitude to some inspiring role models: Franz Pfeiffer who first introduced me to X-ray imaging 8 years ago as a Bachelor student. Without your encouragement and support I would not be working in this field today. David Paganin who dedicated many hours discussing speckle imaging with me, which was very inspirational and encouraging.

I would like to thank all the kind people who helped with proofreading of this thesis: Irene, Pierre, Nick, Xiaowen, Nghia, Malte and Vincent. Thanks a lot, your comments substantially helped to improve the thesis.

Finally, I would like to thank my family and friends in Germany, the UK and various other places in the world, for their ongoing support, love and encouragement during these past years that have not always been easy. I wouldn't have made it to this point without you! A special thanks goes to my boyfriend for the great support during the last stages of preparing this thesis. Thanks for dealing with all my stressfulness, tears and late nights working. I wouldn't have gotten through these tough past weeks without your help!

Contents

Abbreviations

1D	One dimenisional
2D	Two dimensional
3D	Three dimensional
AO	Aorta
AV	Aortic valve
C	Carbon
Ca	Calcium
CCD	Charge-coupled device
CDI	Coherent diffractive imaging
CMOS	Complementary metal-oxide-semiconductor
COR	Cortex
CRL	Compound refractive lens
CT	Computed tomography
CTF	Contrast transfer function
DCM	Double-crystal monochromator
DCMM	Double-crystal multilayer monochromator
ED	Estimated embryonic day
ERFC	Gaussian error function
ESRF	European Synchrotron Radiation Facility
ESRF-EBS	ESRF extremely brilliant source
FBP	Filtered back-projection
FCC	Fluid catalytic cracking
FPS	Fourier power spectrum
FWHM	Full width at half maximum
Ga	Gallium
GBI	X-ray grating-based imaging
GPU	Graphics processing unit
H&E	Haematoxylin and eosin

H_2O	Water
HREM	High-resolution episcopic microscopy
ID	Insertion device
IM	Inner medulla
In	Indium
ISOM	Inner stripe of the outer medulla
IVS	Interventricular septum
LIGA	X-ray lithography and electroplating
linac	Linear accelerator
LSF	Line spread function
LV	Left ventricle
MACE	Metal-assisted chemical etching
microCT	Micro-computed tomography
MLM	Multilayer monochromator
MRI	Magnetic resonance imaging
MTF	Modulation transfer function
MTRI	Masson’s trichrome
MuCLS	Munich compact light source
MV	Mitral valve
NOM	Nanometer optical metrology
OSOM	Outer stripe of the outer medulla
PA	Pulmonary artery
PAS	Periodic acid-Schiff
PBS	Phosphate buffered saline
PET	Polyethylene terephthalate
PFA	Paraformaldehyde
PM	Phase modulator
PMMA	Polymethyl methacrylate
PS	Polystyrene
PSF	Point spread function
PV	Pulmonary valve
PVC	Polyvinyl chloride
RA	Right atrium
ROI	Region of interest
RV	Right ventricle
SBI	X-ray speckle-based imaging
sCMOS	Scientific complementary metal-oxide-semiconductor
Si	Silicon
Sn	Tin
TIE	Transport of intensity
Tukey	Tapered cosine
UMPA	Unified modulated pattern analysis

XFEL	X-ray free electron laser
XGI	X-ray grating interferometry
XPCI	X-ray phase-contrast imaging
XSS	X-ray speckle scanning
XST	X-ray speckle tracking
XSVT	X-ray speckle-vector tracking

Chapter 1
Introduction

We shall see what we shall see. We have the start now; the developments will follow in time. Dam (1896)

This is the answer W. C. Röntgen reportedly gave when asked about the future of X-rays, which he had just discovered in 1895. And he was right. Since these early days, X-rays have been subject to rapid developments in terms of imaging techniques as well as applications, both areas of intense ongoing research to this date. This Ph.D. thesis is part of this actively progressing field. It presents work contributing to the development and optimisation of emerging X-ray imaging techniques, namely X-ray speckle-based and grating-based phase-contrast imaging, as well as demonstrations of the potential of these methods for existing and new areas of applications.

1.1 Background, Motivation and Present Work

The X-ray images taken by Röntgen were based on exploiting the absorption of X-rays by the object to visualise its inner structure, which is nowadays called absorption-based X-ray imaging. This conventional way is still the main workhorse of X-ray imaging and used in a large number of applications such as medical diagnostic imaging, security screening, non-destructive testing, foreign body detection in medicine and food production, and many more.

Absorption-based X-ray imaging relies on the fact that for a fixed wavelength the absorption of X-rays in a specimen depends on its composition, density and thickness. This, in fact, had already been observed by Röntgen in his very first experiments (Röntgen 1898). As a consequence, high-density materials such as metals or bone lead to strong X-ray absorption while low-density materials such as plastics or biomedical soft tissue only attenuate the X-ray beam very weakly, in particular at higher energies. It is hence relatively easy to distinguish materials with large differences in density based on X-ray absorption, but small density variations in a specimen are difficult

M.-C. Zdora, *X-ray Phase-Contrast Imaging Using Near-Field Speckles*,
Springer Theses, https://doi.org/10.1007/978-3-030-66329-2_1

to visualise. A prominent example is the visualisation of biomedical specimens. Bones can easily be distinguished from surrounding soft tissue, as observed early in Röntgen's images of his assistant's and wife's hands, whereas differences in the soft tissue itself cannot be visualised with sufficient contrast.

This limitation is addressed by X-ray phase-contrast imaging, introduced 70 years after Röntgen's early work (Bonse and Hart 1965). Instead of measuring the absorption in the sample, the X-ray phase-contrast imaging approach exploits the phase shift of the X-rays as they travel through the specimen. It has been demonstrated that utilising the phase information can significantly increase image contrast between features of similar densities, in particular for biomedical soft tissue (Fitzgerald 2000; Momose et al. 1996). Furthermore, X-ray phase-contrast imaging has the potential to lead to better dose efficiency, a crucial factor for medical imaging applications (Lewis 2004). This is due to the fact that the X-ray phase-shift cross-section drops less rapidly with the X-ray energy than the absorption cross-section. This allows for the use of higher X-ray energies, which leads to a reduction in the dose absorbed by the sample. Since it was first introduced, X-ray phase-contrast imaging has found a large range of applications originally mainly for medical and biomedical imaging, but later also in other areas such as materials science, geology and archaeology, as well as metrology (for the characterisation of X-ray optics) and wavefront sensing (for the analysis of the X-ray beam itself).

Different methods have been proposed to extract the X-ray phase-shift information about the sample. They all rely on translating the phase shift into intensity variations in the observation plane, which can be recorded by a detection system, as will be explained in more detail in the next chapter of this thesis. Some of the methods not only deliver the phase-contrast image but also complementary X-ray transmission and small-angle scattering information from the same data set. The latter is commonly referred to as dark-field signal in this context (Nesterets 2008; Yashiro et al. 2010).

Among these multimodal techniques, X-ray grating interferometry (David et al. 2002; Momose et al. 2003; Weitkamp et al. 2005) has gained popularity in the imaging community during the last decade due to its quantitative character, high phase sensitivity and compatibility with low-brilliance polychromatic X-ray sources that allowed for its translation to the laboratory (Pfeiffer et al. 2006) and raises hopes for its future implementation in the clinics. The principle of X-ray grating interferometry is to use an X-ray beam-splitting grating to create a periodic interference pattern downstream in the detection plane, which is then used as a wavefront marker. The information on the specimen is encoded in modulations of this reference pattern arising when the sample is inserted into the beam path. These are subsequently decoded computationally to extract the transmission, refraction and small-angle scattering signals of the sample from the change in intensity, the lateral displacement and the change in visibility of the reference pattern, respectively.

A similar idea is the basis for the most recently proposed phase-sensitive (and multimodal) imaging method, namely X-ray speckle-based imaging (Bérujon et al. 2012a, b; Morgan et al. 2012). The periodic grating pattern is replaced by a random pattern, known as X-ray near-field speckle pattern (Cerbino et al. 2008). The latter is produced by placing a diffuser, i.e. a material containing small randomly distributed particles, into the X-ray beam, which leads to X-ray scattering and interference effects. X-ray speckle-based imaging has raised great attention in the last years as it can reach a very high phase sensitivity down to a few nanoradians angular resolution and can be operated with a simple setup that does not require additional specialised equipment and is compatible with polychromatic and divergent beams. Commonly, cheap and widely available sandpaper is used as a diffuser, making this method significantly less costly than many other methods.

These two phase-sensitive imaging methods are the subject of this Ph.D. thesis, which explores X-ray phase-sensitive imaging with a single, periodic or random, phase modulator (grating or diffuser) as a wavefront marker to access the phase-contrast and other complementary multimodal signals of a sample under investigation. The approach of using a single phase modulator allows for an easily implemented, flexible experimental setup that has the potential for wider uptake by the user communities, also at X-ray laboratory sources and in clinical environments. The main focus of the project is the further development and optimisation of the relatively young X-ray speckle-based imaging technique, exploring advanced data acquisition and reconstruction approaches, but also demonstrating its potential for a range of applications. The latter include high-contrast, quantitative phase-contrast and multimodal imaging in the fields of biomedical research, geology and materials science, in particular in three-dimensional (3D) tomographic implementation, as well as X-ray optics characterisation. In addition to the studies and developments on the speckle-based technique, X-ray grating interferometry using a single grating was investigated and optimised for biomedical imaging applications. Although the process for creating the interference pattern and the commonly applied algorithms for signal extraction differ for X-ray grating interferometry and speckle-based imaging, both share the same basic principles of signal generation. In fact, it will be shown in this thesis that the two approaches can be unified in a single data acquisition and reconstruction method, which was developed during this Ph.D. project. This bridges the gap between grating- and speckle-based methods and generalises the concepts discussed in this thesis to any kind of reference pattern, making it transferable to most existing setups designed for X-ray phase-contrast imaging. Moreover, the approach can be extended to laboratory sources, which makes it widely accessible for research applications and future clinical and industrial use.

1.2 Outline of this Thesis

This thesis contains the results of newly developed concepts and experimental validations of X-ray single-grating and X-ray speckle-based phase-sensitive imaging. It is organised as follows.

Chapter 2 gives an overview of the fundamental principles of X-ray imaging that are essential for the work presented later in the thesis. Starting from the basics of the interaction of X-rays with matter, the concepts and implications of temporal and spatial coherence are explained, followed by a summary of different X-ray phase-contrast imaging methods. For the latter, a more detailed overview of the techniques relevant to this thesis is given. In the last sections of the chapter, the principles of computed tomography as well as a summary of different types of X-ray sources, in particular the ones used during this Ph.D. project, is given.

Chapter 3 provides some basic information on the layout, specifications, instrumentation and equipment of the two synchrotron beamlines at which most of the experiments during this Ph.D. project were carried out: beamline I13 at Diamond Light Source (UK) and beamline ID19 at the European Synchrotron Radiation Facility (France). At the end of the chapter, the contributions to these beamlines resulting from this Ph.D. project are summarised.

Chapter 4 presents results on X-ray grating interferometry with a single grating. It starts with the theoretical background on the working principles, signal generation and extraction and developments of X-ray grating interferometry, followed by the demonstration of X-ray single-grating interferometry at Diamond I13 beamline for high-contrast 3D biomedical imaging. In the last section of the chapter, more recent results on the implementation of single-grating interferometry at I13 are shown.

Chapter 5 contains a comprehensive literature review of the concepts and state of the art of X-ray speckle-based imaging. Starting from the principles of X-ray near-field speckle and its use as a wavefront marker, the image formation and reconstruction processes are explained and the existing experimental implementations are outlined. Furthermore, an overview of the developments and applications of X-ray speckle-based imaging to date is given, including some most recently reported advances.

Chapter 6 introduces the unified modulated pattern analysis (UMPA), which unifies the X-ray grating- and speckle-based imaging techniques in a single approach and is one of the main developments achieved during this Ph.D. project. The chapter starts with a section exploring the performance and limitations of existing operational modes for speckle-based imaging. This is followed by the first demonstration of UMPA, which is shown to address some of the main limitations of previous implementations of the speckle- and grating-based techniques. After introducing the principles of UMPA data acquisition and analysis, the potential of the method for multimodal imaging is experimentally demonstrated and quantitatively analysed on a test sample and a more complex specimen. It is, moreover, shown that UMPA can be applied not only to random speckle but also periodic reference patterns. The last section of the chapter contains a more detailed study of the tunable character of UMPA and an analysis of the effects of different scan and reconstruction parameters on the image quality.

In Chap. 7, the UMPA approach implemented with both a random and a periodic reference pattern is applied to X-ray optics characterisation for the analysis of two different X-ray refractive lenses. Aberrations in the focussing behaviour due to previous beam damage and fabrication errors are successfully identified and quantified using UMPA phase-sensitive imaging.

Chapter 8 presents another major contribution of this project to the field of X-ray speckle-based imaging: the first speckle-based phase tomography of a scientifically relevant specimen using UMPA, demonstrating its potential for biomedical imaging.

UMPA phase tomographies of various unstained biomedical soft-tissues samples, such as a mouse testicle, a mouse kidney and human brain tissue, are shown and evaluated qualitatively as well as quantitatively. An in-depth analysis of the results on the murine kidney illustrates the great potential of X-ray speckle-based phase tomography for 3D virtual histology, giving unprecedented insights into the interrelationship and connectivity of features within fully hydrated biomedical specimens without the need for contrast agents.

Chapter 9 reports on some of the recent and ongoing work conducted during this Ph.D. project that is aimed at making X-ray speckle-based imaging adaptable to various different experimental conditions and setups and widening its accessibility to the user community. This includes the optimisation of setup components and the extension of the method to higher X-ray energies as well as polychromatic, low-brilliance laboratory X-ray sources. A new type of customisable speckle diffuser is presented, which has the potential to optimise the imaging setup by adapting the speckle properties to specific experimental conditions. Furthermore, high-energy speckle imaging with the UMPA technique is demonstrated on volcanic rock and mortar samples, extending the technique to new areas of research. In the last section of the chapter, the translation of UMPA to a laboratory X-ray system is reported and its performance is illustrated in a proof-of-principle measurement of a test sample and a bug.

The thesis ends with Chap. 10, which contains a summary and conclusions of the work presented in the previous chapters and a guide of which phase-sensitive imaging method might be most suitable for given experimental conditions. The chapter closes with a discussion on future developments and perspectives.

1.3 Contributions

The main work conducted during this Ph.D. project and presented in this thesis, is based on ideas and concepts conceived by the author and her primary supervisors Dr. Irene Zanette and Prof. Pierre Thibault. Further work was performed in collaboration with a number of European research groups, some on topics pursued in this thesis, some not directly related. The major part of the research within this project is focussed on X-ray grating- and speckle-based imaging. This involved collaborations with several people, in particular for beamtime support and for the supply and preparation of samples. Their contributions are mentioned in the relevant sections. For the parts of this thesis based on previously published papers, collaborators are not explicitly mentioned but can be found in the author list of the related publications.

Specifically, the contributions of the Ph.D. candidate to the main projects presented in this thesis are summarised in the following:

- *Implementation and applications of X-ray grating interferometry at Diamond I13-2 (Chap. 4)*: The project was initiated by Dr. Irene Zanette and continued by the Ph.D. candidate. Planning and experiments were led by the Ph.D. candidate and measurements were performed with the assistance of beamline staff and collaborators. The specimens were prepared and provided by collaborators. All data analysis was performed by the Ph.D. candidate.

- *Development of the unified modulated pattern analysis (UMPA) for speckle- and grating-based imaging (Chap. 6)*: The initial idea of the UMPA data acquisition and analysis method and the first version of the basic Python code were conceived by Prof. Pierre Thibault and Dr. Irene Zanette. The Ph.D. candidate parallelised and optimised the code and carried out first performance tests. All experiments using UMPA were initiated, planned and led by the candidate with input from her supervisors. Beamline staff and collaborators provided beamtime support and samples. Data analysis was performed by the candidate.
- *Optics characterisation with the unified modulated pattern analysis (Chap. 7)*: The initial idea for characterising refractive lenses was proposed by the Ph.D. candidate in discussion with collaborators Dr. Frieder Koch and Dr. Arndt Last. Experiment planning and measurements were led by the candidate with support from beamline staff and collaborators. Collaborators provided the samples and information on them. All analysis was performed by the candidate.
- *3D virtual histology with the unified modulated pattern analysis (Chap. 8)*: The idea was conceived by the Ph.D. candidate. The experiments were planned and led by the candidate with support from beamline staff and collaborators. The data analysis was performed by the candidate. Some analysis steps, such as the 3D visualisation of the reconstructed data, videos and the conventional histology procedure, were carried out with support from collaborators, as indicated in the relevant sections. Samples were prepared and provided by collaborators.
- *Development of customisable phase modulators (Chap. 9, Sect. 9.2)*: The principle of customising phase modulators for speckle-based imaging was conceived by the Ph.D. candidate together with the collaborator Dr. Joan Vila-Comamala. Dr. Joan Vila-Comamala had the idea of using the technique of metal-assisted chemical etching and produced the phase modulators. The experiments were planned and carried out by the Ph.D. candidate and the collaborator with support from beamline staff. The sample was provided by Dr. Johannes Ihli. Data reconstruction was performed by the Ph.D. candidate.
- *Investigation of geological and materials science samples (Chap. 9, Sect. 9.3)*: The experiment was initiated and planned by collaborators Dr. Tunhe Zhou and Dr. Beverley Coldwell. The measurements were carried out by the Ph.D. candidate together with the collaborators and with support from beamline staff. The samples and information on them were provided by Dr. Beverley Coldwell and Dr. Fei Yang. Analysis of the data presented in this thesis was performed by the Ph.D. candidate.
- *First implementation of the unified modulated pattern analysis at a laboratory source (Chap. 9, Sect. 9.4)*: The laboratory setup with the liquid-metal-jet X-ray source was conceived by the Ph.D. candidate's supervisor Prof. Pierre Thibault. The experimental arrangement and procedure for lab-based UMPA speckle imag-

ing were developed and planned by the candidate in discussion with Dr. Irene Zanette and Prof. Pierre Thibault. The experiment was led by the candidate and carried out with support from collaborators as listed in Sect. 9.4. All data analysis was performed by the candidate.

In addition to the measurements and results presented in the following chapters, collaborative work on X-ray grating interferometry was performed at Diamond I13 and ESRF ID19 beamlines with the group of Prof. Bert Müller, Biomaterials Science Centre at the University of Basel (Switzerland), mainly for imaging of brain tissue. This resulted in a number of co-authored conference proceedings, see Schulz et al. (2016, 2017), Khimchenko et al. (2016). Further work on the development of X-ray speckle-based imaging was conducted in collaboration with Dr. Tunhe Zhou and Jenny Romell, first at the liquid-metal-jet laboratory X-ray source at KTH Stockholm (Sweden) in the group of Prof. Hans Hertz and later at Diamond I13 and Diamond I12 beamlines (UK), leading to co-authored publications, see Zanette et al. (2014), Zanette et al. (2015), Zhou et al. (2015), Zhou et al. (2016), Romell et al. (2017). In another collaboration, both speckle- and grating-based imaging were used for high-speed differential phase-contrast imaging at ESRF ID19 beamline for the visualisation of fast processes. This research was carried out with Dr. Patrik Vagovič, DESY and XFEL (Germany) and Dr. Margie Olbinado, ESRF (France), as evidenced in Olbinado et al. (2018); Vagovič et al. (2019).

Although not discussed in this thesis, the author was also involved in experiments and data analysis using X-ray single-distance propagation-based (inline) phase-contrast imaging to investigate biomedical and palaeontological specimens. Propagation-based phase-contrast measurements were performed in a collaboration with the group of Prof. Bert Müller, Biomaterials Science Centre at the University of Basel (Switzerland), for the high-resolution visualisation of human brain tissue and further analysis such as cell quantification, as reported in resulting articles, see Hieber et al. (2016); Khimchenko et al. (2016, 2017). The aim of another project in collaboration with Dr. Irvin Teh and Prof. Jürgen Schneider, previously Radcliffe Department of Medicine, University of Oxford (UK), now Leeds Institute of Cardiovascular & Metabolic Medicine, University of Leeds (UK), was the high-contrast, high-resolution visualisation of rat and mouse heart tissue for the validation of diffusion-tensor magnetic resonance imaging (MRI) data. The results have been published as Teh et al. (2017, 2018). The third biomedical application of propagation-based imaging during this Ph.D. project was a collaboration with Dr. Carles Bosch Piñol and Prof. Andreas Schaefer, Francis Crick Institute London (UK), on the visualisation of the murine olfactory tube in the brain, which is an essential part of the olfactory sensory system.

Apart from biomedical imaging, contributions in the scope of this Ph.D. project include propagation-based phase-contrast imaging of palaeontological specimens in collaboration with the group of Prof. Roger Benson, Department of Earth Sciences, University of Oxford (UK). In this project, X-ray phase-contrast imaging at high spatial resolution was used to visualise osteocytes, i.e. bone cells, in a large number of fossilised fish bone samples from different points in time to study the evolution of the cell size in bony fishes.

Moreover, the author of this thesis was involved in work on absorption-based micro computed tomography of biomedical specimens based on staining with contrast agents, which she had initiated during her Bachelor project in the group of Prof. Franz Pfeiffer at Technical University Munich (Germany). This resulted in a co-authored journal publication, see Bidola et al. (2019).

A list of the first and co-authored publications derived from the main work and collaborative side projects conducted during this Ph.D. project can be found in the author's Curriculum Vitae at the end of this book. It also includes a list of invited and contributed talks by the Ph.D. candidate given at international conferences, workshops and meetings.

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Chapter 2
Principles of X-ray Imaging

X-rays are electromagnetic radiation emitted by electrons outside the nucleus of atoms. They typically have energies in the range of 100 eV to 500 keV, corresponding to a wavelength range from 2.5 pm to 10 nm (Als-Nielsen and McMorrow 2011). Compared to visible light, X-rays have a much higher penetration power through dense materials and in particular hard X-rays (with an energy of >10 keV) have the ability to penetrate deep into matter. This was first observed by Röntgen when he discovered X-rays in 1895 (Röntgen 1895, 1898). X-rays were immediately used to investigate the inner structure of materials as well as the human body and they have been exploited for various imaging applications ever since.

While the first applications of X-rays were based on their absorption in the material, e.g. for medical imaging of bones (Codman 1896; Editorial 1896b, a; Spiegel 1995), it was discovered later that, analogous to the visible light case (Zernike 1942, 1955), also their phase shift can be exploited for signal generation (Bonse and Hart 1965). However, the extraction of phase-contrast information is not as straightforward as for absorption imaging as detectors can only measure the beam intensity, and not the phase shift. Therefore, methods were developed to encode this information in intensity variations that could be recorded by the detector. The first X-ray phase-contrast setup was proposed in 1965 by Bonse and Hart (Bonse and Hart 1965) who built a crystal interferometer to visualise the X-ray phase shift. However, X-ray phase contrast only gained increased interest with the development of powerful and coherent X-ray sources at the end of the 20th century. In particular, the discovery of X-ray propagation-based phase-contrast imaging at the European Synchrotron Radiation Facility (ESRF) was a major milestone in the popularity of the X-ray phase-contrast modality (Snigirev et al. 1995, 1996; Raven et al. 1996). An interesting fact here is that both the first discovery of X-rays by Röntgen and the first discovery of propagation-based phase contrast happened by chance when the researchers were investigating on a different topic. Röntgen was performing experiments with a Crookes tube and noticed the green fluorescence light on the phosphor screen covering the tube, which was caused by X-rays generated in the tube. X-ray

M.-C. Zdora, *X-ray Phase-Contrast Imaging Using Near-Field Speckles*,
Springer Theses, https://doi.org/10.1007/978-3-030-66329-2_2