Large field of view, fast and low dose multimodal phase-contrast imaging at high x-ray energy

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X-ray phase contrast imaging (XPCI) is an innovative imaging technique which extends the contrast capabilities of ‘conventional’ absorption based x-ray systems. However, so far all XPCI implementations have suffered from one or more of the following limitations: low x-ray energies, small field of view (FOV) and long acquisition times. Those limitations relegated XPCI to a ‘research-only’ technique with an uncertain future in terms of large scale, high impact applications. We recently succeeded in designing, realizing and testing an XPCI system, which achieves significant steps toward simultaneously overcoming these limitations. Our system combines, for the first time, large FOV, high energy and fast scanning. Importantly, it is capable of providing high image quality at low x-ray doses, compatible with or even below those currently used in medical imaging. This extends the use of XPCI to areas which were unpractical or even inaccessible to previous XPCI solutions. We expect this will enable a long overdue translation into application fields such as security screening, industrial inspections and large FOV medical radiography – all with the inherent advantages of the XPCI multimodality.

X-ray imaging is one of the most widespread inspection/diagnostic techniques, mainly because of its simplicity and low cost. Its principles are straightforward: an x-ray source irradiates a sample, and an x-ray detector placed on the opposite side collects the transmitted photons. In general, x-rays allow the investigation of the internal features of opaque objects because of their reduced interaction with matter compared to electromagnetic radiation at longer wavelengths. This capability is widely exploited in application fields such as security screening, industrial inspections and medical diagnosis. While improvements have been introduced on the technical side, the basic principle of x-ray imaging has remained unchanged. In the last decades, however, x-ray phase contrast imaging (XPCI) has emerged as a new technique with the potential to improve the conventional x-ray imaging through a radically different principle. XPCI systems are sensitive to the x-ray phase-shift induced by the sample; this is described by &delta; in the complex refractive index n = 1 − &delta; + i&beta;, while the x-ray attenuation is related to &beta.. Compared to attenuation, the phase contrast effect is significantly stronger for low Z materials (Z < 10, e.g. soft tissues), and it does not decrease as dramatically with increasing energy (E). XPCI is therefore considered an ideal candidate for applications involving low-Z materials, which generate a weak signal in conventional x-ray imaging. Moreover, XPCI could improve the applications where high x-ray dose could be an issue, since it allows to reduce it by increasing E while preserving high image contrast.

XPCI was first introduced by Bonse and Hart in 19651, but became the subject of worldwide interest with the advent of ‘3rd generation’ synchrotron radiation facilities2–5. Wilkins et al. demonstrated the possibility to perform XPCI using a conventional x-ray micro-focus source6, opening the way to a wider use in research. In the last decade, several XPCI techniques have been adapted and refined to be effective using conventional sources7–9. An important feature of most XPCI systems is their capability to simultaneously provide both attenuation and differential phase contrast (DPC) images, which makes conventional attenuation-based images still available when an XPCI setup is used. Moreover, a third contrast channel, often called dark-field (DF), can also be made available.
performed XPCI at 160 kVp using a steel wool as the OE, over a FOV of 5.29. They retrieving the phase information by using setups based on high magnification, as shown by Wang et al. provide images of large objects (up to 20 cm)24, then by Ignatyev et al. imaged a human knee at 90 kVp by stitching 17 small (15 mm × 35 mm) FOV images. An alternative approach consists in removing the need for precise OEs and retrieving the phase information by using setups based on high magnification, as shown by Wang et al.26. They performed XPCI at 160 kVp using a steel wool as the OE, over a FOV of 5 × 4 cm; however, this requires either a synchrotron or a microfocal source.

To the best of our knowledge, currently there are no conventional x-ray tube-based XPCI systems capable of simultaneously providing the following three desired features: 1- high x-ray energy; 2- large FOV and 3- fast acquisition time. While possibly some dedicated XPCI setups can be optimized to satisfy one or two of those characteristics, so far the simultaneous realization of all three seemed to be a technical impossibility. Applications fields such as baggage screening and industrial inspections could benefit enormously from an ‘ideal’ XPCI system, because they tend to require fast imaging of large and dense objects. Importantly, access to higher energies for GI and tens of microns for EI, respectively. At the moment, the relatively small pitch and aperture size of those absorbing OEs (a few microns for GI and tens of microns for EI, respectively) are limiting the thickness of the absorbing material (and therefore the accessible x-ray energy), because of the limitations in the maximum achievable aspect ratio, in particular for large FOV OEs. For this reason, XPCI applications are mostly limited to small objects imaged using small FOVs at low x-ray energies. As a consequence, several XPCI groups are trying to overcome those limitations. Tubes operated at 100 kVp were used first by Donath et al. (on a FOV of approximately 3 × 2 cm)24, then by Ignatyev et al. with a 6 × 6 cm2 FOV25; Thüring et al. proposed an edge-on approach for the OE, which allowed the use of a tungsten tube at 160 kVp at the cost of an extremely reduced FOV in one direction (a single detector line) and long acquisition time (6 minutes per line)26. Sarapata et al. exploited a round OE of 10 cm in diameter to perform a Computed Tomography at 70 kVp27, and Horn et al. imaged a human knee at 90 kVp by stitching 17 × 18 small (15 mm × 35 mm) FOV images. An alternative approach consists in removing the need for precise OEs and retrieving the phase information by using setups based on high magnification, as shown by Wang et al.26. They performed XPCI at 160 kVp using a steel wool as the OE, over a FOV of 5 × 4 cm; however, this requires either a synchrotron or a microfocal source.

In this paper we present a multimodal XPCI prototype based on EI that simultaneously satisfies all three key requirements outlined above through the development of an application-oriented XPCI system. This system can provide images of large objects (up to 20 × 50 cm2) up to 100 kVp30, and can be operated in ‘low-statistics’ mode to obtain XPCI images of acceptable quality at 2.5 mm/s with a conventional x-ray source operated at only 2 mA. The prototype exploits the advantages of EI’s simple geometry (i.e. the x-ray masks’ large pitch and aperture size). The resulting relaxed aspect ratio allows realizing thicker structures, thus improving the quality of the OEs at high energy and relaxing the alignment requirements at the same time. The use of the asymmetric EI scanning solution18 eliminates the need of re-positioning any of the OEs during the acquisition to obtain the multimodal images; at the same time, it allows large FOVs. The system is flux efficient, because it allows for the use of a relatively large focal spot without additional source collimation e.g. source gratings. This guarantees good image quality also during a fast scan using a relatively low-power x-ray source. The system is also dose-efficient thanks to the use of low-absorbing graphite substrates.

**Results**

A simplified scheme of the system is depicted in Fig. 1a. It requires two additional OEs if compared to conventional x-ray imaging setups. The x-ray beam is shaped by the pre-sample mask (M1) into small fan-shaped beamlets, which are aligned with the apertures of the detector mask (M2). The intensity curve in Fig. 1b (called Illumination Curve, IC) is obtained for each detector column by scanning M1 along the x-axis. In the asymmetric mask configuration11, each beamlet hits the detector mask on a different position, corresponding to a different value of the IC. In this way, only a lateral scan of the object is needed to obtain all the information necessary to retrieve absorption, DPC and DF images, and no movement of the OEs is required11,12. The masks alignment in x, z, θ and ϕ is straightforward13, and was observed to be stable over several days of operations. Periodic checks (once every several acquisitions) of the M1 x-position are sufficient to guarantee artefact free images. This procedure is performed automatically when no samples are in the FOV.
A first example of the system capabilities is shown in Fig. 2. Three complementary images of a full-sized computer keyboard were simultaneously obtained through a single 196 s scan at 80 kVp. The scan time can be significantly reduced further as explained in the discussion section, by using different equipment components.
which are however already available on the market. This shows easy adaptability to fast scanning of a variety of large objects in non-destructive testing and security applications. A second example aimed at demonstrating potential for low dose, full-field medical imaging (as an option for future development), is shown in Fig. 3. Here two example acquisitions of a standard Ackermann mammographic phantom are shown. The first three panels show a full, multimodal scan yielding absorption (a), DPC (b) and DF (c) images of the phantom obtained with an overall entrance dose of 2 mGy. Panel (d) shows a possible alternative use of the scanner in which multimodality is sacrificed in exchange for additional dose reduction through the use of a ‘single shot’ retrieval algorithm. In this case the entrance dose was only 0.15 mGy. These values should be compared with typical entrance dose levels of 10–12 mGy delivered in standard clinical mammography. Note that an additional 2.4 cm Plexiglas layer was added to the phantom to reach an overall realistic thickness of 4.7 cm.

It should also be noted that the presented examples are aimed at demonstrating the capabilities of the system; specific applications of those capability will then have to be investigated and optimized on a case-by-case basis.

Discussion
The developed system allows for the first time performing XPCI on large FOVs using a high-energy beam in a short acquisition time. The optimized use of EI was key to solve most of the technical limitations. One of the key reason is EI’s inherent technical simplicity compared to other approaches. The main factor contributing to this simplicity is the relatively large pitch (70–100 μm; matching the detector pixels pitch) and aperture size (10–30 μm) in the OEs. For the same aspect ratio, this allows increasing their gold thickness, thus improving the technique’s effectiveness at higher x-ray energies. It also makes the system much more robust against instabilities and easier to align. Those are important features for applications such as security screening or industrial quality controls, where the time spent to realign the system translates into a loss in efficiency/productivity since throughput is key. The large feature size in the OEs also made it easy to align three smaller masks in order to obtain a system with larger FOV, with negligible “blind” areas between the individual elements. Minimal artefacts due to some residual misalignment among the individual mask elements are noticeable though a careful investigation. A second crucial advantage came from the asymmetric EI implementation. Typically, XPCI requires repositioning and/or scanning one of the OEs and acquiring several frames to obtain the data necessary for retrieving the DPC and DF information. In asymmetric EI, only the sample scan is required while everything else remains stationary. This allows speeding up the acquisition and simplifying the entire process. EI is also an efficient technique in terms of dose delivery. The absorbing first mask protects the sample from the unused parts of the direct beam, meaning that the sample is irradiated only by the fan-shaped beamlets. This makes the system well suited for dose-critical applications in medical screening and diagnostic procedures.

As an example of the system capabilities, a large common object was scanned at high energy in approximately 3 minutes (Fig. 2). It should be noted that the tube current was only 2 mA, leaving ample margin for additional increase in scanning speed. Moreover, a total of 128 detector columns were used, and speed can also be increased by using a larger number of detector columns thus matching full use of the cone beam. This system therefore makes DPC and DF available at high energy and over large FOVs in short exposure times, allowing a
straightforward translation of XPCI in fields such as security screening, industrial inspections, medical screening (chest, dental, breast, possibly even full-body radiography), which were all not accessible with XPCI before. Our results also open the possibility to explore the benefits of XPCI mammography at higher energy, which can lead to very significant dose reductions as recently demonstrated by a pilot study with synchrotron radiation. The low-dose x-ray images shown in Fig. 3 provide preliminary evidence that it may be possible to add to the information available with conventional mammography (i.e. attenuation), by making DPC and DF images available while still operating at a reduced dose compared to current clinical standards. The latter image has been proved beneficial for enhanced diagnosis. Additional very significant dose reductions can be obtained using a single-shot phase-retrieval algorithm, which provides a phase map of the object (Fig. 3d), under sample homogeneity assumptions which are well met by breast tissue.

It should also be noted that further improvements of the setup are still possible. For example, the x-ray tube was operated at 160 W, about an order of magnitude below standard practice in XPCI where tube powers above 1 kW are normally used, including with comparable focal spots. Such a source could be used to speed up the acquisition, increase image quality or for a combination of both. The focal spot could also be extended along one direction without significant negative effects in the (orthogonal) direction of phase sensitivity, and it has recently been demonstrated that the use of multiple sources (obtained e.g. by sectioning a larger source, similarly to what done in grating interferometry when a "source grating" is used) is also possible. Another gain in photon flux can be achieved by reducing the distance between the source and the detector (currently at 2 m), and higher statistics can be achieved by increasing the number of detector columns used to create the final images (currently 128 or 1.28 cm, which does not cover the whole available beam cross-section). Energy can be further increased if higher aspect ratio masks (>10:1) are used, which can for example be obtained by adapting and optimizing metal-assisted chemical etching silicon techniques already in use for the small OEs in GE, where exceptionally high aspect ratios of gold structures such as 16:1 have been produced.

In summary, we have designed, built and tested the first system capable of high energy, large FOV and fast XPCI. So far XPCI has been used mainly at low energies, small FOV and required slow acquisitions, which restricted its application remit to research projects. The development presented in this paper allows XPCI applications which were not possible before. Importantly the new system can be straightforwardly adapted for use in a real-world application through minimum engineering investment, thus realising a long-awaited commercial translation of XPCI.

It should be noted here that much faster acquisitions are routinely achieved at synchrotron radiation facilities, however here the focus is on translational aspects, which make the use of conventional sources mandatory.

Methods

Asymmetric Edge Illumination. In ‘classic’ EI the x-ray beam is shaped in thin fan beamlets by a highly absorbing gold pre-sample mask (M1 in Fig. 1a) with symmetric apertures. Each beamlet is aligned with a second (detector) mask (M2 in Fig. 1a) with matching apertures; every beamlet aperture pair combination corresponds to a detector column. A lateral scan of M1 provides a bell-shaped IC (Fig. 1b) for each pixel. This has a maximum when corresponding apertures are aligned and two close-to-zero minima for full misalignment at the left and right hand sides of the maximum. An object placed between M1 and M2 has three effects on the IC: 1- absorption, changing the area below the IC; 2- DPC, changing the position of the IC maximum; 3- DF, changing the width of the IC. The retrieval of absorption, DPC and DF requires at least three images acquired at different positions of the IC. In asymmetric EI, subgroups of apertures in M1 are slightly laterally shifted from their symmetric positions. In this way, each detector column provides a full object image on a specific position of the IC through an object scan, without the need to move any of the OEs. The shifted aperture subgroups were designed in such a way that every sub-group will acquire images at one of the points highlighted with circles in Fig. 1b. Images from columns belonging to the same sub-group are then summed together to increase the statistics, and fed to the retrieval algorithm, ultimately providing attenuation, DPC and DF images.

Experimental system. The system was designed making use of experimentally validated Monte Carlo simulations with the goal of optimizing the output for absorption, DPC and DF. It was built inside a stand-alone lead-shielded cabinet at the Nikon Metrology UK’s factory in Tring, Hertfordshire, UK. It is based on a Tungsten X-Tek 160 tube with a focal spot tuned to be approximately 80 μm. M1 and M2 masks are placed at 1.5 m and 1.95 m from the source, respectively. The two masks are realized by electroplating a 200 μm of gold on 500 μm thick graphite substrates. Both large masks are a combination of 3 smaller masks carefully aligned and fixed on a steel frame. The resulting sizes are 1.2 × 15 cm² for M1, and 1.5 × 20 cm² for M2. The detector is a dual-energy single photon counter Cd-Te CMOS (XC Counter XC-FLITE FX2) with 2048 × 128 square pixels 100 μm in side, placed 2 m from the x-ray source. The two masks frames are mounted on two separate 4-axis stepper motor turrets for alignment. Apertures are 21.4 μm and 28 μm for the smaller and the larger mask, respectively, with their projected pitches matching the detector pixels (i.e. actual pitches are 75 μm and 97.5 μm respectively). Apertures in M1 are arranged in asymmetric groups of four, in order to generate 4 separate images on the IC in a single object scan (see Fig. 1b). The shifts are: -s, 0, s and 2 × s with s = 10 μm. The system’s spatial resolution in the vertical direction is determined by the detector’s effective pixel (75 μm), or any of its multiples if used in rebinned mode. The resolution in the scanning direction can be tuned by varying the scanning speed and the acquisition frame rate, with a minimum equal to the aperture sizes in M1 i.e. 21.4 μm.

Samples and acquisition parameters. The keyboard in Fig. 2 is a standard wireless keyboard (Microsoft Wireless Keyboard 800; 46 × 16 cm²). The source was set at 80 kVp and 2 mA without filters. The detector acquisition rate was 32 Hz and the acquisition speed was 2.5 mm/s, leading to a total scan time of 198 s. The effective
acquisition resolution is 75 μm × 75 μm. The relatively high resolution in the acquisition is needed to detect the edge-enhancement peaks. Images can then be resized after data reconstruction. For example, images in Fig. 2 are rebinned to 600μm × 600μm. To downsize the differential phase image, a selective sampling to preserve minima and maxima was performed as opposed to rebinning: note however that the reported acquisition time corresponds to the original acquisition with 75 μm step. The second sample is the Ackermann mammographic phantom (RMI 160; Gammex, Middleton, WI, USA) with size 10 × 11 × 2.3 cm³, which contains a series of simulated lesions. It has been acquired together with a 2.4 cm PMMA slab to simulate a realistic compressed breast thickness of 4.7 cm. For this application, we tested the system using two different settings. In the first case (Fig. 3a, b and c), the tube was set at 80 kVp and 2 mA, and the beam was filtered with 1 mm of Al. The effective pixel in the acquisition was 75 μm × 75 μm. The x-ray entrance dose was 2 mGy, as measured using a calibrated and certified dosimeter (UNIDOS E PTW – Universal dosimeter equipped with a soft x-ray chamber type 23344). The second acquisition (Fig. 3d) used an x-ray beam at 56 kVp, a current of 2 mA and 1 mm of Al filtration. This time the effective pixel in the acquisition was 37.5 μm × 75 μm. Both acquisitions had a total scan time of approximately 12 minutes. It should be noted that the increased scan time is due to the desire to reach clinically significant doses with the low dose rate provided by the used source. This is not only due to its limited power (see comments above), but also to the relatively high x-ray energy employed in this case compared to a standard (Molybdenum) mammographic spectrum. We simulated an acquisition at a lower entrance dose using only one of the 4 images from the asymmetric groups of apertures. In this case the entrance dose was 0.15 mGy (Fig. 3d). Conversely, the samples in Figs 2 and 3a, b and c were acquired using images from all 4 symmetric positions on the IC (two on one side and two on the other as shown in Fig. 1b). This choice of points simplifies the reconstruction formulas while providing sufficiently high image quality.

Data reconstruction. The raw data from each column of the detector are flat-fielded using images recorded without the sample before and after each sample scan. Images from each of the 4 groups of apertures (corresponding to the different asymmetric values: -s, 0, s and 2 × s, see above) are then shifted and added together to increase statistics (with a total of 32 images per asymmetric group). The used retrieval algorithm is an adaptation to the 4-points case of the method first proposed by Rigon et al. for analyser-based imaging and later extended to GI. Following the same formalism, the 4 normalized images obtained (Ij) can be expressed as a second order Taylor expansion for the IC, R(φ + ΔφR + Δφs) around φ, where ΔφR is the refraction angle and Δφs is the stochastic scattering angle:

\[
I_j = I_0[R_j + \frac{1}{2}R_j\Delta\phi_R + \frac{1}{2}R_j\Delta\phi_R^2 + \frac{1}{2}R_j\Delta\phi_s^2], \ j \in [1, 4]
\]

(1)

Here, Rj, Rj, and Rj are the value, the first derivative and the second derivative of the IC calculated at the point φ, respectively. I0, ΔφR, and Δφs are the pixel-wise absorption, DPC and DF signals induced by the imaged object, respectively. The 4-equations system can be solved to obtain:

\[
I_R = \frac{1}{2}I_1 + I_2 + I_3 + I_4
\]

(2)

\[
\Delta\phi_R = \frac{(I_1 + I_2) - (I_3 + I_4)}{I_1 + I_2 + I_3 + I_4} - \frac{R_j}{R_j}
\]

(3)

\[
\sigma_{\Delta\phi_s}^2 = 2\frac{R_j(I_1 + I_2) - R_j(I_3 + I_4)}{R_j(I_1 + I_2)} - \Delta\phi_s^2
\]

(4)

In analogy with the cited work by Rigon et al., the following assumptions were made: - small refraction and DF angles, symmetric images on the IC with images 1 and 4 at ±50% of the IC. We note that those assumptions are satisfied in most practical cases, especially at high x-ray energies like those employed in this study, since they lead to smaller refraction and DF angles. However, alternative approaches such as IC fitting can be used in situations where those assumptions are not fulfilled. The ultra-low x-ray dose image in Fig. 3d was processed accordingly to the algorithm presented by Diemoz et al. starting from a single image on the IC (beamlet 1 in Fig. 1b). The image represents the phase map of the object.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author Contributions
A.A., M.E., I.H. and A.O. conceived the study. A.A. designed the system with inputs from M.E. and A.O. A.A., B.P. and I.H. built the system. A.A. collected the data. A.A., F.A.V. and P.C.D. analysed the data. A.A. and A.O. wrote the manuscript. All authors reviewed the manuscript.

Additional Information
Competing Interests: A.A., M.E., F.A.V., P.C.D. and A.O. declare no competing financial interests. B.P. and I.H. are Nikon employees.

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