Flexible solutions for lab-based phase contrast and dark field CT and micro-CT

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Abstract

Phase-based (PB) x-ray imaging (XRI) methods have grown in importance over recent years, and it can probably be argued that the majority of micro-CT experiments at synchrotrons include phase effects in some form or fashion. A comparable if not higher level of interest has consequently arisen with regards to the translation of PB XRI into lab-based CT and micro-CT system, where however things have been moving more slowly, and the opposite is probably true i.e. most acquisitions are currently non-PB. The reasons for this are multiple and varied, but the key ones may be attributable to setup complexity and to the necessity to move optical elements during acquisitions, limits in spatial resolution, and excessively long acquisition times. In the imaging of biological tissues, especially *in vivo*, excessive delivered dose can pose an additional concern. Based on the acceptance that a "one size fits all solution" probably does not exist, and that most real world applications typically do not require all the above features simultaneously, our group has focused on the development of a *flexible* approach where typically counteracting features (e.g. high spatial resolution and fast acquisition times) can be traded off, including while making use of the same imaging system after this has been designed and built. This paper briefly reviews the technical innovations that have made the above possible, presents some key results in various areas of application, and discusses areas currently undergoing further development, among which are extensions to both higher and lower energy x-ray spectra, and new approaches to multi-modality and data retrieval.

Keywords: x-ray phase contrast, dark-field imaging, micro-CT, edge-illumination, single-shot phase retrieval

1 Background

Following Bonse and Hart's pioneering experiments with crystal-based interferometers in the mid-60s [1], PB XRI underwent very significant expansion in the mid-90s, notably with the advent of 3rd generation synchrotron sources. Most effort was directed towards free-space propagation methods [2], which were rapidly demonstrated to work also with non-synchrotron sources so long as the focal spot was small enough [3], and towards crystal-based methods [4, 5], less sensitive to larger focal spot dimensions [6], but effectively imposing the use of monochromatic radiation. In both cases, use with conventional sources was therefore possible, but imposed lengthy acquisitions either because a very small focal spot had to be used, or because only a very limited bandwidth was exploited while most of the polychromatic spectrum was filtered out. About ten years later, methods emerged that enabled the use of more extended, larger bandwidth sources. Talbot-Lau interferometry [7] uses a "source grating" to slice an extended source into an array of mutually incoherent, but individually coherent sources. This enables a considerable extension of the focal spot, the only limit being the reduced spatial resolution it induces because of blurring at the detector plane. Although the method exploits the Talbot self-imaging effect which is intrinsically energy dependent, the tolerable bandwidth is considerably extended with respect to crystal methods

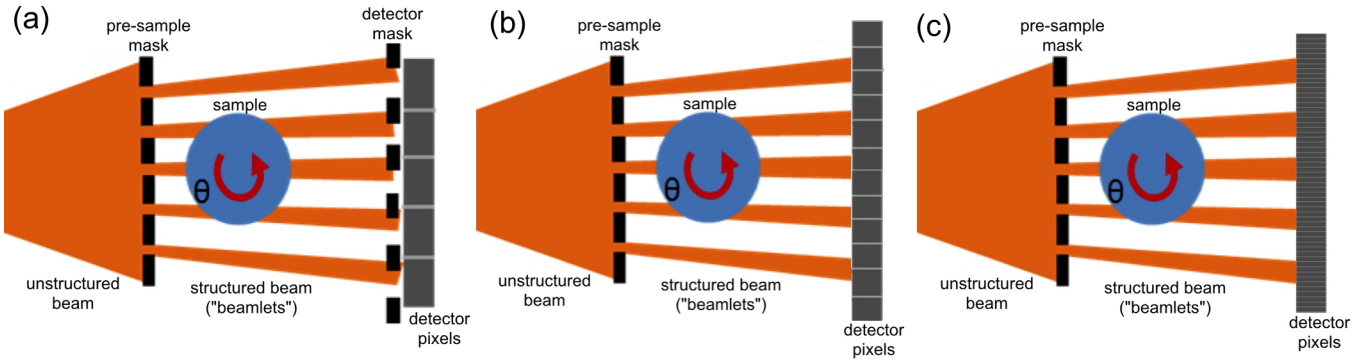

Figure 1: Schematic of the "Edge Illumination" method subject of this paper. A first masks splits the incoming beam into a plurality of beamlets, which then go through the sample. Interactions with the sample change intensity, direction and width of the beamlets, analysis of which leads to attenuation, differential phase, and dark field images respectively (see text). Beamlet changes can be analysed by introducing a second ("detector") mask as shown in panel (a), by hitting the separation between adjacent pixels (b), or by using a detector with a sufficiently small pixel to resolve the beamlets directly (c).

"Edge Illumination" (EI) [8], the method this article focuses on, uses an absorbing mask before the imaged sample, which splits the incoming x-ray beam. The sample is therefore hit by an array of individual, separated beamlets rather than by a uniform "flood" field. However, the beamlet separation is sub-pixel and therefore, mask and detector defects aside, an image acquired in the absence of a sample appears perfectly flat; moreover, in CT sample rotation ensures undersampling-related errors on phase retrieval are minimized [9]. Distortions in the individual beamlets are then analysed either by placing a second mask on the detector [8,10], by using a detector with sufficient resolution ("beam tracking", [11]), or by aligning the beamlets so that they straddle adjacent pixels if these have a sufficiently sharp point spread function (e.g. with direct conversion detectors, [12]). These three implementations are schematically represented in panels (a), (c) and (b) of figure 1, respectively. Analysis of the beamlets then yields attenuation through their dampening, differential phase from their deflection, and ultra-small angle scattering (USAXS – often referred to as "dark field") through their broadening [13]. Early experiments showed that this allows strong phase signals and effective phase retrieval also with relatively large (e.g. 100 μm) focal spots and unfiltered polychromatic beams [8,10]. Moreover, the method was proven to be totally achromatic [14]. The presence of an absorbing mask upstream of the sample means unnecessary dose delivery is avoided; indeed, the method is 100% dose efficient in the "beam tracking" [11] and "pixel straddling" [12] setups, and can be made up to 80-90% dose efficient also with the "double mask" set up by using small apertures in the pre-sample mask and limited misalignment between the two masks [15]. While there might be a misconception of limited flux efficiency due to the presence of at least one absorbing mask, it should be noted that the relatively large pitch and moderate aspect ratio makes it easy to realize substrate free masks which, combined with the method's achromaticity and the fact that no source aperturing is needed, means x-rays are often used more efficiently than in other methods subject to absorption in substrates and/or spectral filtration, or which use source collimators.
Following the introduction of Talbot-Lau and EI, additional methods were introduced, and occasionally adapted for use with non-synchrotron sources (e.g. [16]), although these typically require small focal spots along similar principles as in free-space propagation methods. A series of reviews was recently published which present detailed discussions of the various PB approaches and their evolution [17-21].

2 Built for speed: single-shot phase retrieval

A single frame collected with a system like the one depicted in Fig 1(a) will contain a mixture of attenuation, differential phase and dark field contributions. Although we have started to develop methods that, under special conditions, enable the retrieval of more than one contrast channel from a single input image [22], broadly speaking multiple input frames are required to separate phase, attenuation and dark field images. Still with reference to Fig. 1(a), scanning the pre-sample mask vertically in sub-pixel steps in the absence of a sample results in the collection of a bell-shaped curve, with a maximum corresponding to the position where the apertures are aligned, and a minimum where they are completely misaligned. In the absence of major mask defects and neglecting small possible changes in the perceived focal spot size resulting from viewing it from slightly different angles, this curve ("Illumination Curve", IC) is the same for all pixels, and it fully characterises the EI system, in the same way as the "rocking" curve characterises crystal-based methods [5]. Indeed, our early phase retrieval approaches [10] were modelled on the pioneering "diffraction enhanced imaging" algorithm described in [5]: Chapman *et al*. combine two images acquired on opposite sides of the crystal rocking curve, and we do the same with images acquired on either side of the IC, corresponding to two different displacements of the pre-sample mask. If a dark field image is required alongside phase and attenuation ones, then a third frame is collected at a third position of the mask [13], again in analogy with work initially developed in the framework of crystal-based methods (see e.g. [23]).
This does not tie in well with high-speed tomography, as it inherently implies displacing an optical element (in our case the pre-sample mask) in multiple positions for each angular projection, which prevents a continuous rotation of the sample thus lengthening scan times. While the "beam tracking" approach [11] shown in Fig 1(c) removes this limitation, because analysing the beamlets directly simultaneously yields their intensity, central position and width, it requires the use of a small pixel size to allow resolving the individual beamlets. This limits the available field of view, plus typically detectors with small pixels have low detection efficiencies (due to e.g. the need to use a thin scintillator to limit the lateral light spread), which can lead to longer exposure times. While the use of a larger pixel size can be allowed by introducing a larger magnification, this does not solve the limited field of view issue, plus it imposes the use of a small focal spot which again can lead to excessive exposure times. The same limitations apply to e.g. speckle imaging [16, 21] and other "single grid" methods [e.g. 24]. If only phase and attenuation are required, then the configuration shown in Fig 1(b) can offer a solution; however, it imposes the use of a detector with a very sharp point spread function [12], as is typically provided by direct conversion, photon counting detectors which also do not currently exist in large 2D areas. Another limitation arises from the fact that every second pixel must be "skipped" (see Fig. 1(b)), which reduces spatial resolution hindering the use of e.g. selenium-based flat panels.
Indeed the key advantage of the setup represented in Fig 1(a) is that it allows the use of any commercial detector, be it direct and indirect conversion, with any pixel size, as well as of relatively large focal spot sizes (~100 μm) so long as large magnifications are not employed; we see this as a key point in terms of enabling commercial translation using source and detector technology which is currently available off-the-shelf.
A first attempt to speed up acquisitions using the "double mask" set up of fig. 1(a) was based on the "reverse projections" principle [25]. This was also initially developed for crystal-based methods [26], and later on adapted to Talbot interferometry [27]. The key idea is that, so long as the centre of rotation is carefully positioned with respect to the detector mask, projections

acquired at angles α and $180 + \alpha$ are equivalent to projections acquired at angle α on corresponding but opposite sides of the IC. This allows keeping the mask at a fixed position (e.g. at 50% intensity on one side of the IC), performing a 360^{o} rotation of the sample, and using the second half of the dataset as complementary frames required to perform the phase retrieval according to the method described in [10] (or equivalent, e.g. [28]). The key advantage of this implementation is that it removes the need for any set-up movement (e.g. pre-sample mask displacement) apart from sample rotation, thus enabling this to be continuous rather that stepped. Used with a detector with negligible readout time (e.g. CMOS-based), this practically eliminates all overheads, and enables a total acquisition time virtually matching the "live" one.
If a quantitative separation of phase and attenuation is not strictly required, even faster scans can be obtained through an adaptation to the EI method of Paganin's pioneering single-shot phase retrieval approach [29]. This enabled us to perform lab-based PB CT scans in record times of a few minutes [30], an example of which is provided in fig. 2.

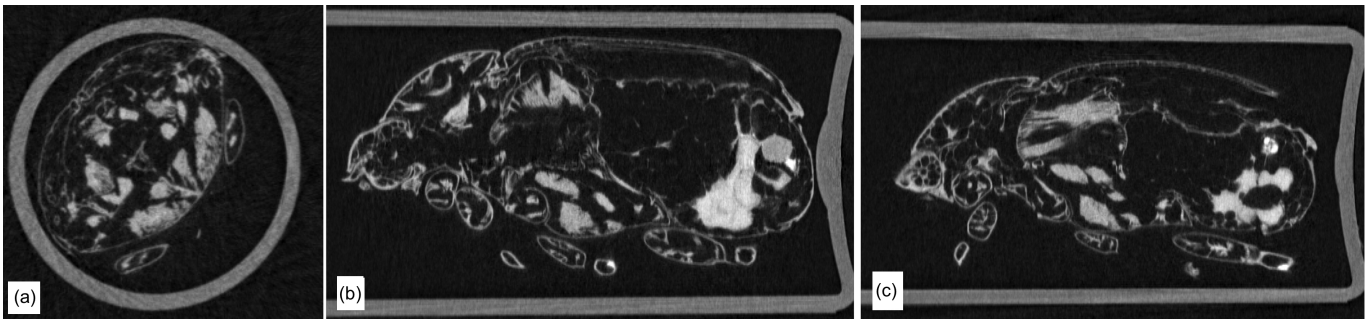

Figure 2: laboratory based, single-shot phase CT of a bug – (a) shows an axial slice, (b) and (c) two different sagittal re-slices. Despite having being collected in approximately 5', phase effects clearly show the soft tissue details inside the insect's body.

The ability to scan samples in just a few minutes enables unprecedented applications, such as intraoperative specimen imaging performed while the patient is asleep on the operating table; indeed, a trial on intra-operative imaging of breast tissue specimens is currently underway.
One caveat is that the "Paganin-based" approach in principle requires the sample to be homogeneous. While this condition is reasonably satisfied by breast tissue specimens, it may prevent extension to more complex objects e.g. if they contain bone. However, as initially observed by Beltram and co-authors [31], the method allows reconstructing individual interfaces between multiple materials one at a time. Hence, the method can be applied repeatedly while targeting different interfaces, and the obtained images can be spliced together to form a high quality image of a more complex object. Through an adaptation of the Beltram approach to the EI method [32], we managed to reconstruct both bones and soft tissues interfaces in a non-uniform biological sample [33] which, together with the method's low-dose capabilities, opens the way to *in vivo* small animal imaging, which is also currently under investigation.

3 Multi-modality and high-resolution

By sacrificing acquisition speed, multimodal images with much higher resolution can be acquired. This exploits the fact that, in EI, resolution is not limited by detector pixel nor focal spot size, but driven by the size of the apertures in the pre-sample mask [34]. Hence stepping the sample in sub-pixel increments ("*dithering*") allows accessing higher resolutions. Coupled with large magnifications, this enables straightforward implementations of the method in microscopy, including at relatively hard x-ray spectra (e.g. 80 kVp, [35]). Initially implemented using the "double mask" approach shown in Fig. 1(a), this high resolution approach was also adapted to the beam tracking method shown in fig 1(c), demonstrating easy access to multimodal (attenuation, phase and dark-field) microscopy both in planar [36] and CT [11] modes. An example of beam-tracking, high resolution PB micro-CT is provided in fig. 3.

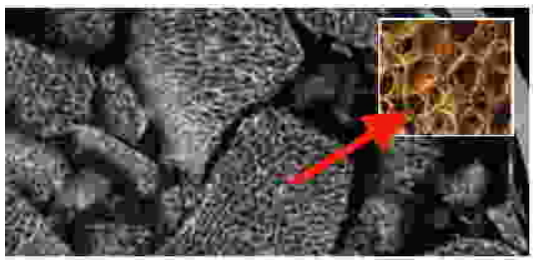
Figure 3: micro-CT of coffee powder showing the internal microporosity of individual powder grains, confirmed by the scanning electron microscope image shown in the inset (individual grains ~ 1mm or below, adapted from [11]).

The important aspect to note is that the "multi-modal, high resolution" use is simply a different acquisition protocol (for a specific description see e.g. [37]) that can be implemented with the same scanner used for "high-speed" acquisitions, e.g. the

"intra-operative" scanner could be used for high resolution, multi-modal digital histology while it is not needed in the operating theatre.

4 Recent developments and future directions

We recently showed that "multi-aperture" EI setups allow combining high phase sensitivity with large dynamic range in USAXS measurements [38], while opening the way to single-shot retrieval of multiple contrast channels [22]. In parallel, we have started to experiment with lab-based focusing of low-energy x-rays to further increase the phase sensitivity in soft matter applications, an example of which is provided in figure 4.

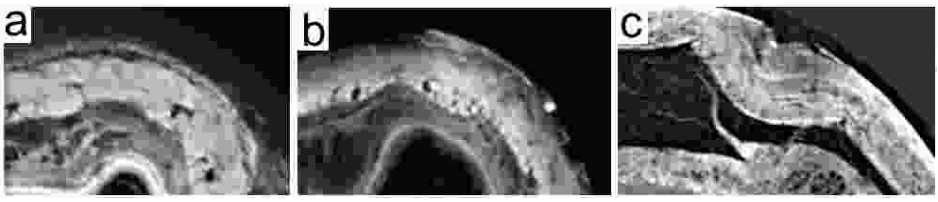

Figure 4: CT slices of oesophageal tissue in which soft tissue differences, invisible to conventional x-rays, are resolved thanks to phase effects. (a) is the synchrotron gold standard, to which the lab-based image in (b) compares favourably; (c) shows additional contrast/resolution achievable through the use of focused soft x-rays.

Another key area of development is adaptation to higher x-ray energies, the proof-of-concept for which was obtained already in the early days of the technology's development [39], to enable exploring denser and higher Z samples that are often crucial in industrial applications. Although we had initially focused our research on industrial inspections to the study of lower-Z samples such as composite materials [40], we have more recently started to exploit the low aspect ratio of our masks to build thick, large area structures. While at the moment this is limited to planar (2D) results (see [41] and example in fig. 5), plans for translation to full 3D imaging are currently being developed.

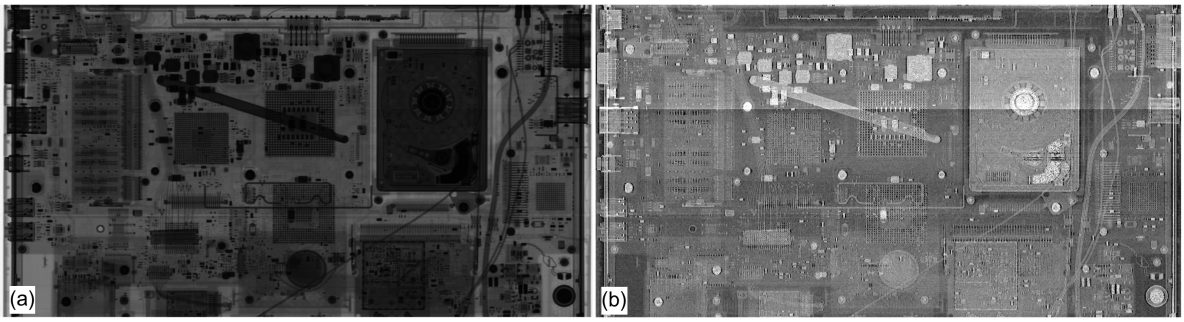

Figure 5: attenuation (a) and dark field (b) images of a whole laptop obtained at 100 kVp with the large area, high x-ray energy scanner described in ref. [41].

We expect the combination of these approaches to enable even more flexibility in our lab-based solutions, opening the way to an even wider range of application across the life and physical sciences, as well as to further industrial translations.

5 Conclusions

Although work remains to be done to further develop the method to adapt it to the specific requirements of the various applications, especially the most challenging ones requiring high x-ray energy and large fields of view ideally coupled with high speed and high resolution, we have shown that the EI approach is sufficiently flexible as to allow trading off different requirements; for example, fast (a few minutes) CT scans can be obtained if "single-shot" retrieval methods are employed, while higher resolution and multi-modal imaging can be accessed in those applications where speed is not essential. This already allows targeting some specific "real world" applications such as intra-operative specimen imaging and some areas of digital histology. We expect continued technical development will make the method increasingly suitable for use in different fields; as far as industrial CT is concerned, 3D scans of low-Z samples like carbon-reinforced plastics are already available and, having demonstrated the ability to penetrate thicker/higher Z objects in 2D, we are now in the process of adapting this to 3D scans as well.

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