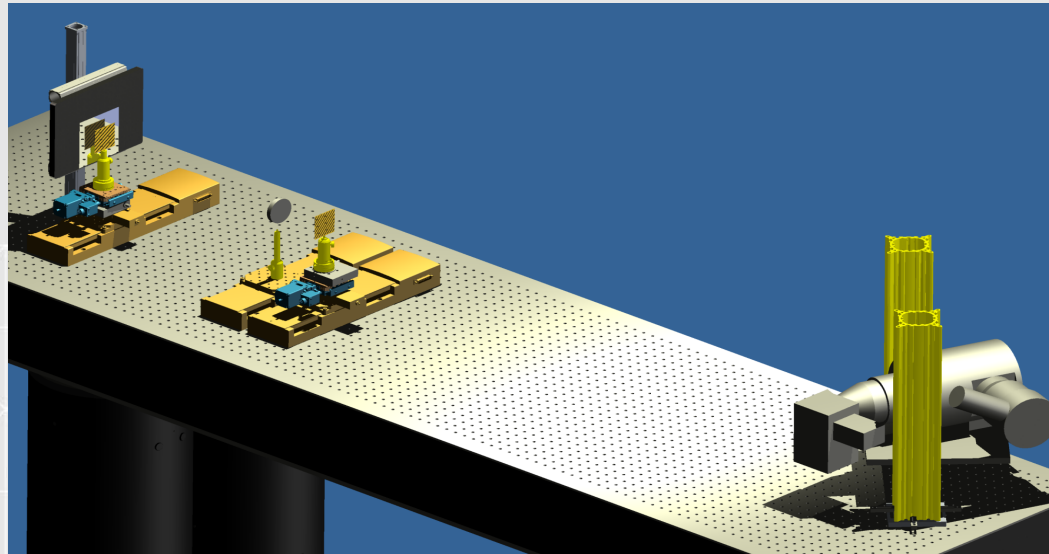


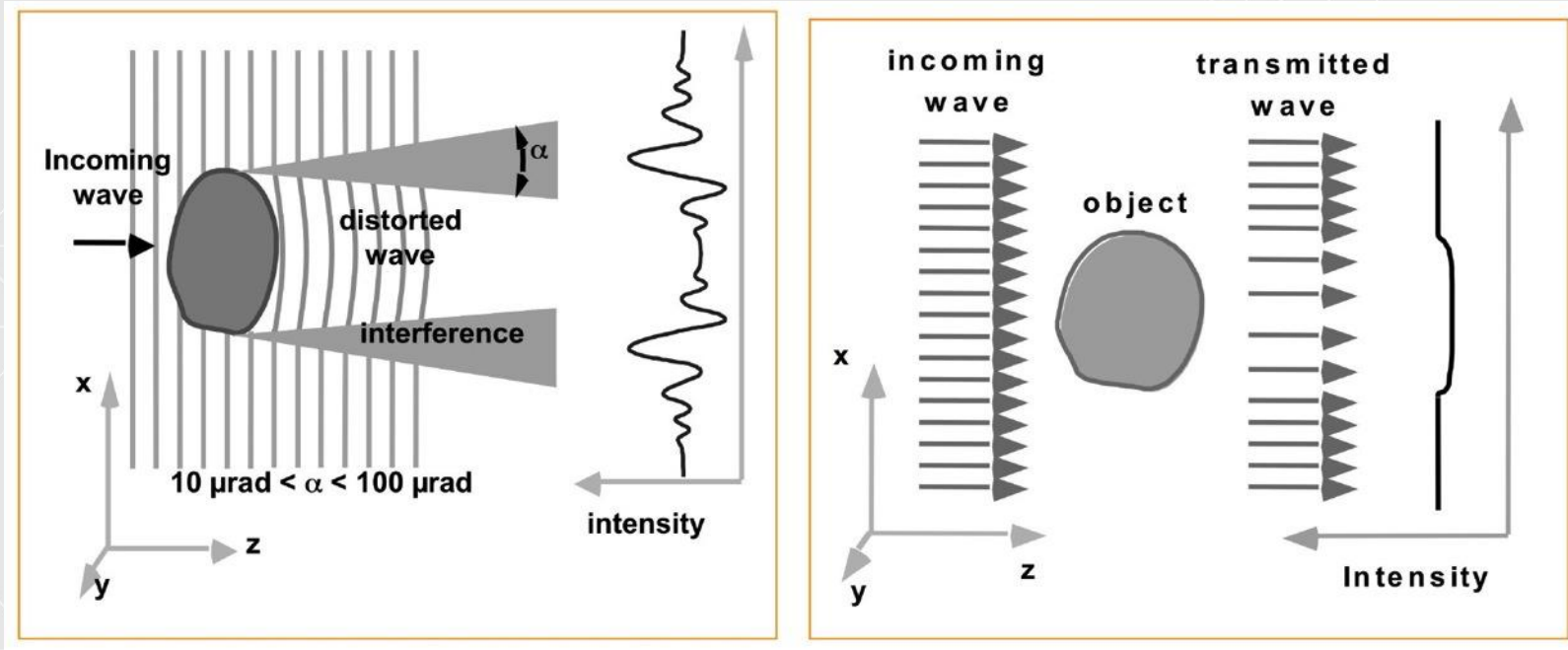


The evolution of edge-illumination X-ray phase contrast imaging and its prospective clinical translation to breast-related applications



Sandro Olivo, Spokesperson, AXIm Group
(<https://www.ucl.ac.uk/medphys/research/axim>)
Medical Physics and Bioomedical Engineering, UCL

Phase Contrast Imaging vs. Conventional Radiology



Refractive index: $n = 1 - \delta + i\beta$; $\delta \gg \beta \rightarrow$

phase contrast ($\Delta I/I_0 \sim 4\pi\delta\Delta z/\lambda$) \gg absorption contrast ($\Delta I/I_0 \sim 4\pi\beta\Delta z/\lambda$)

Two possible approaches:

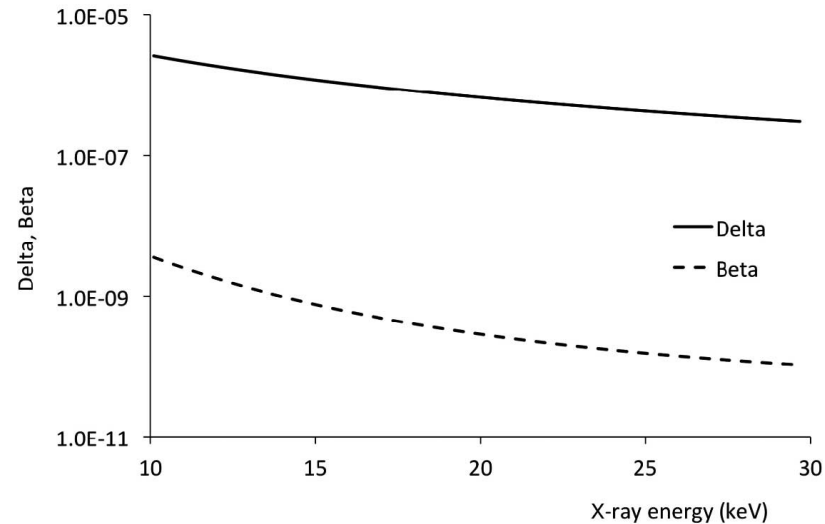
- detect interference patterns
- detect angular deviations

$$n = 1 - \delta + i\beta,$$

$$\mu = \frac{4\pi\beta}{\lambda}$$

$$\Phi(x, y) = \frac{2\pi}{\lambda} \int_{\text{object}} \delta(x, y, z) dz,$$

$$\delta = \frac{r_e \rho_e \lambda^2}{2\pi}$$



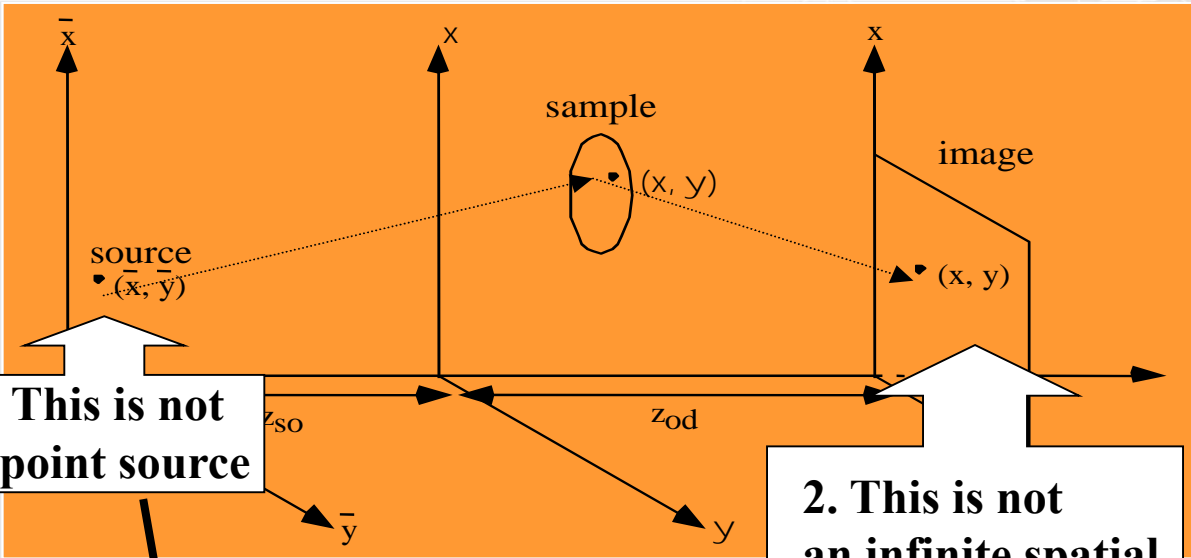
Note 1) ~ 3 orders of magnitude larger
 2) decreases more slowly with x-ray energy

How can we model it?



without the object:

$$E(x, y) = \frac{1}{r} \exp(i2\pi r / \lambda)$$

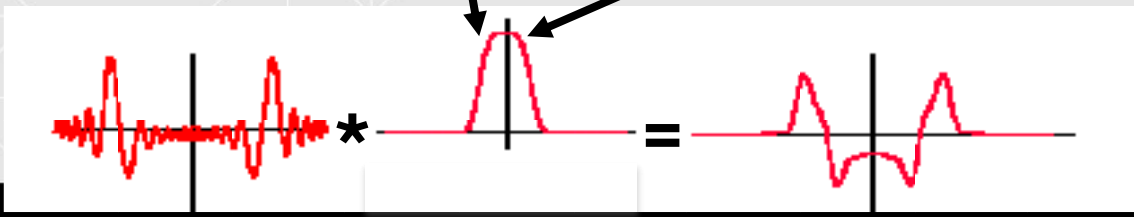


1. This is not a point source

2. This is not an infinite spatial resolution detector

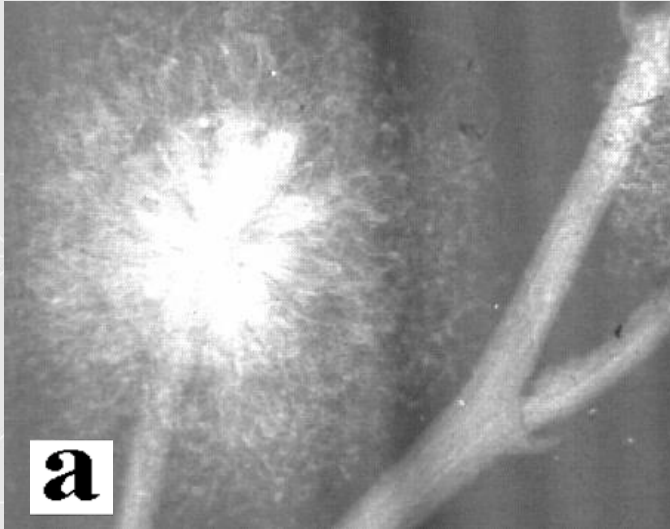
with the object in, it is effectively described by the Fresnel/Kirchoff integral

$$E(x, y) = \frac{1}{\sqrt{i/z_{so}z_{od}(z_{so} + z_{od})}} \exp\left\{\frac{2\pi i}{\lambda} \left[z_{so} + z_{od} + \frac{(y - \bar{y})^2}{2(z_{so} + z_{od})}\right]\right\} \int_{-\infty}^{+\infty} d\bar{x} \exp\left\{\frac{\pi i}{\lambda} \left[\frac{(\bar{y} - x)^2}{z_{so}} + \frac{(x - y)^2}{z_{od}}\right]\right\} \exp[iF(x)]$$

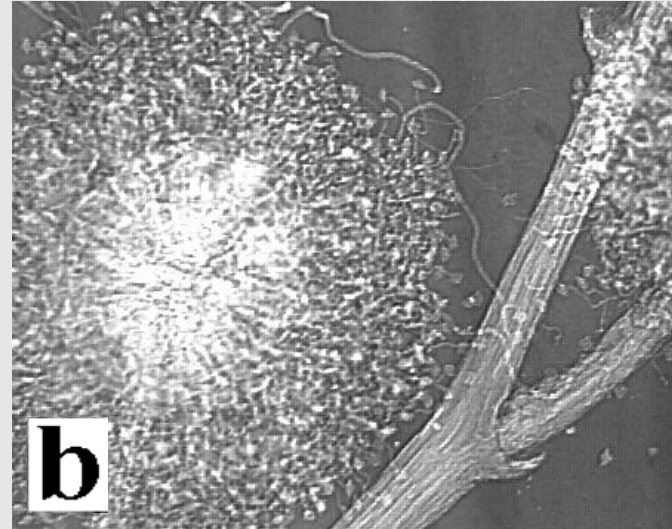




a) absorption

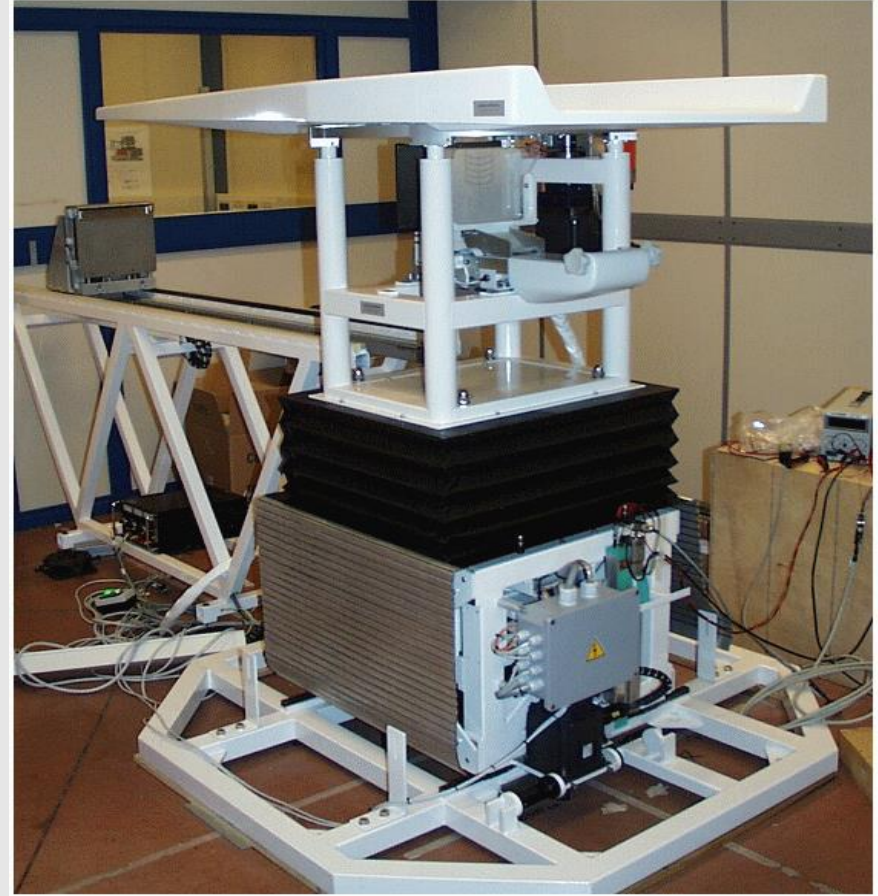
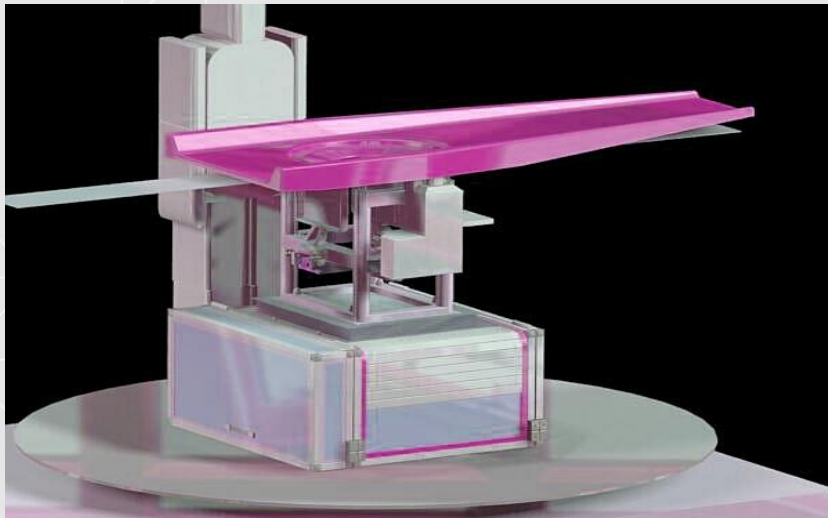
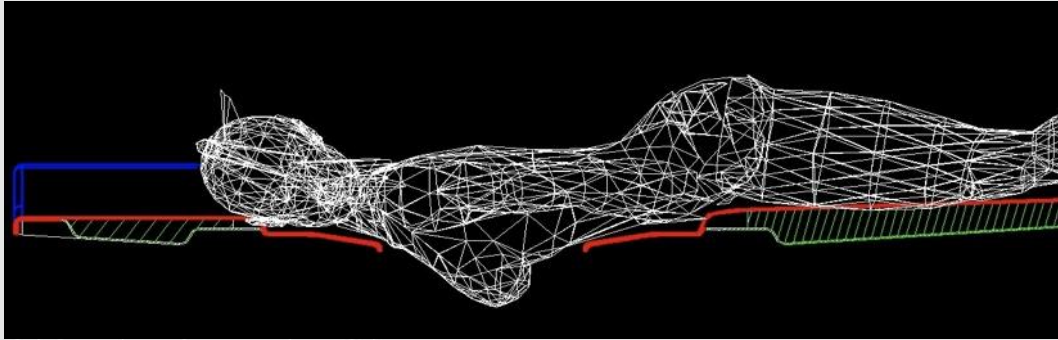


b) phase contrast



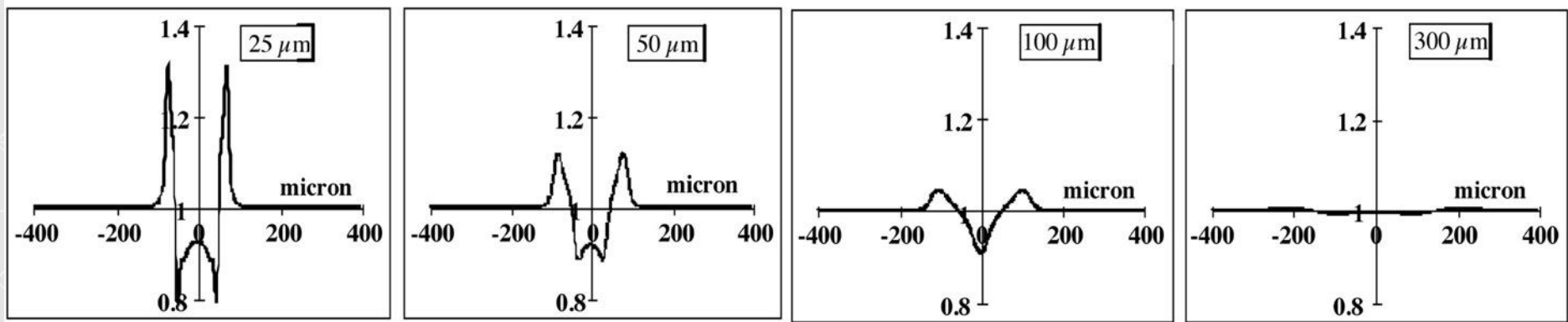


Which led to the realization of a dedicated mammography system in TS



FSP works wonders when implemented with a spatially coherent source – why ask for more?

- It suffers immensely when transferred to conventional sources: the spread associated with projected source size becomes too large and kills the signal.



Moreover:

The system has little flexibility - only d_{sd} can be changed

But:

Amazing stuff @ synchrotrons, e.g. check out Cloetens' work at the ESRF
+ straightforward use e.g. coupled with Paganin's single distance phase retrieval

Remember from a few slides ago: I can also exploit small angular deviations (x-ray refraction)

When crossing an object with negligible absorption ($\beta \sim 0$) but with $\delta \neq 0$, the X-ray wavefield changes from

$$\Psi = \Psi_0 \exp(-ikz)$$

to

$$\Psi = \Psi_0 \exp[i(-kz + \phi)]$$

with

$$\phi(x, y) = -r_e \lambda \int_{\text{object}} \rho_e(x, y, z) dz$$

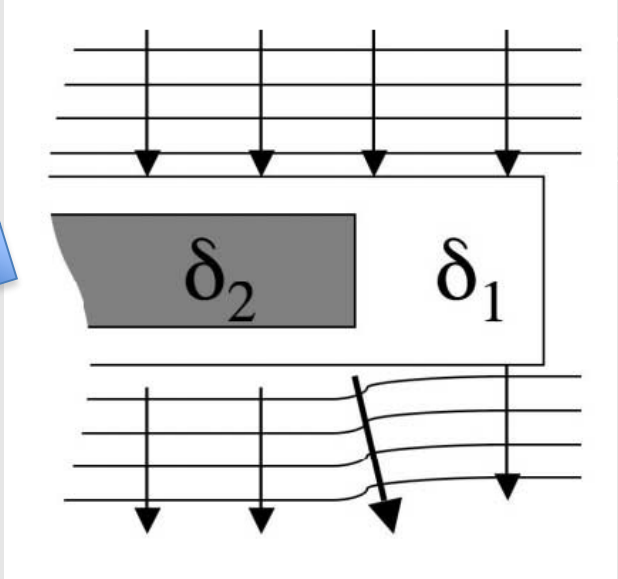
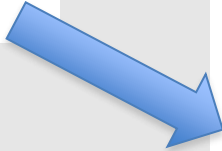
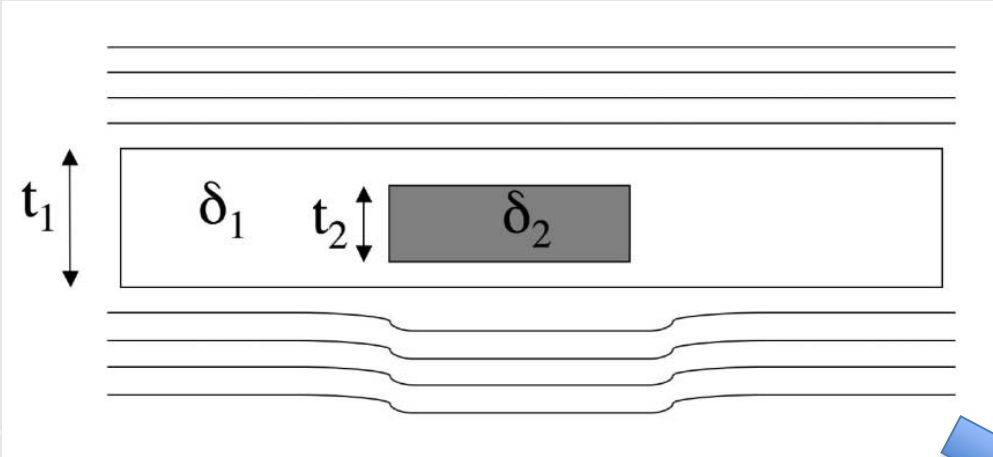
(r_e classical electron radius,
 λ incident radiation
wavelength, ρ_e electron density)

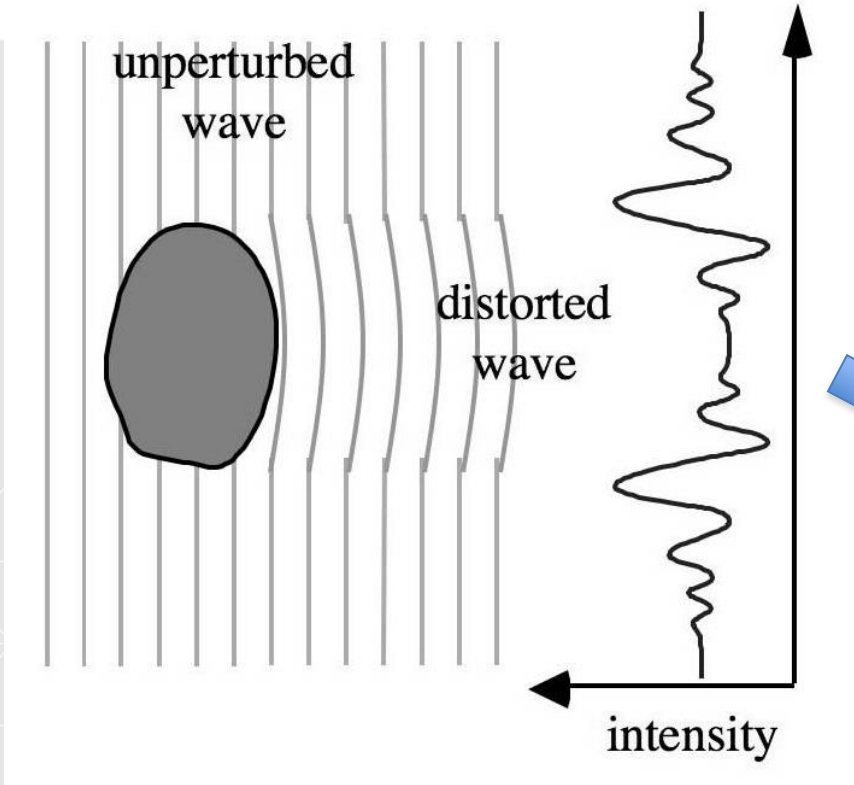
The new wavevector is therefore:

$$\vec{k}' = \left(\frac{\partial \phi}{\partial x}, \frac{\partial \phi}{\partial y}, \frac{2\pi}{\lambda} \right) = \vec{\nabla}_{xy} \phi + k \hat{z}$$

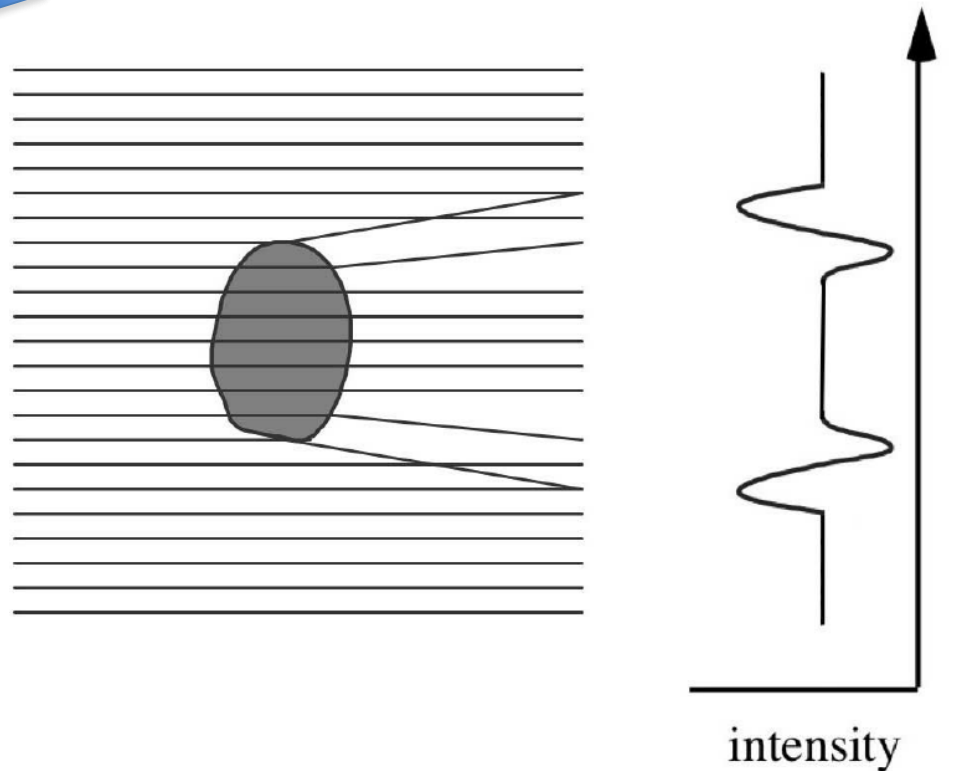
and the angular deviation (relative to the Initial propagation direction) is given by:

$$\alpha \cong \frac{1}{k} \left| \vec{\nabla}_{xy} \phi(x, y, \lambda) \right|$$

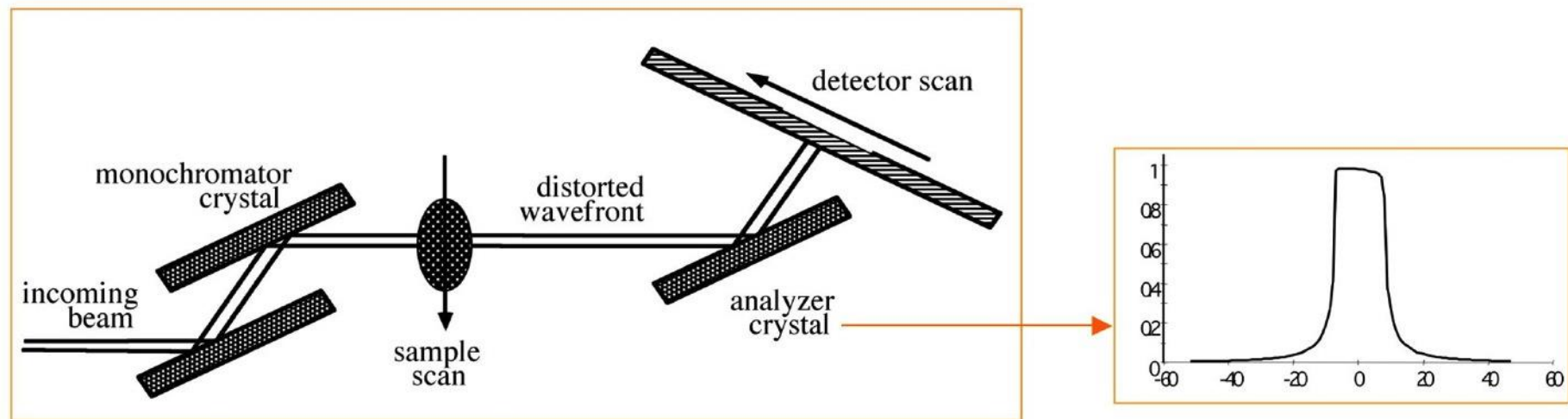




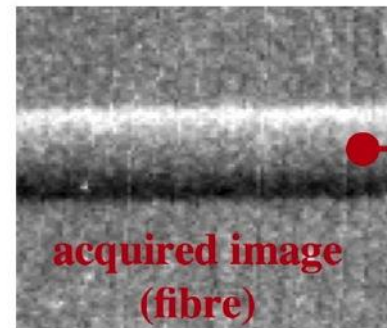
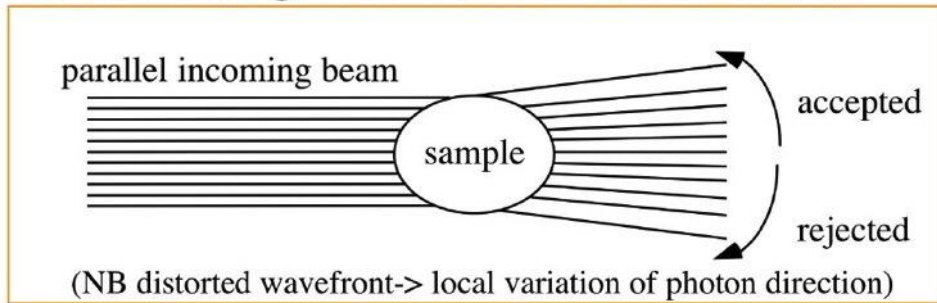
NB you can also model FSP on the same basis; if coherence is relaxed, you will get approximately the same results.



Other methods to perform phase contrast imaging: “Analyzer Based Imaging” (ABI)



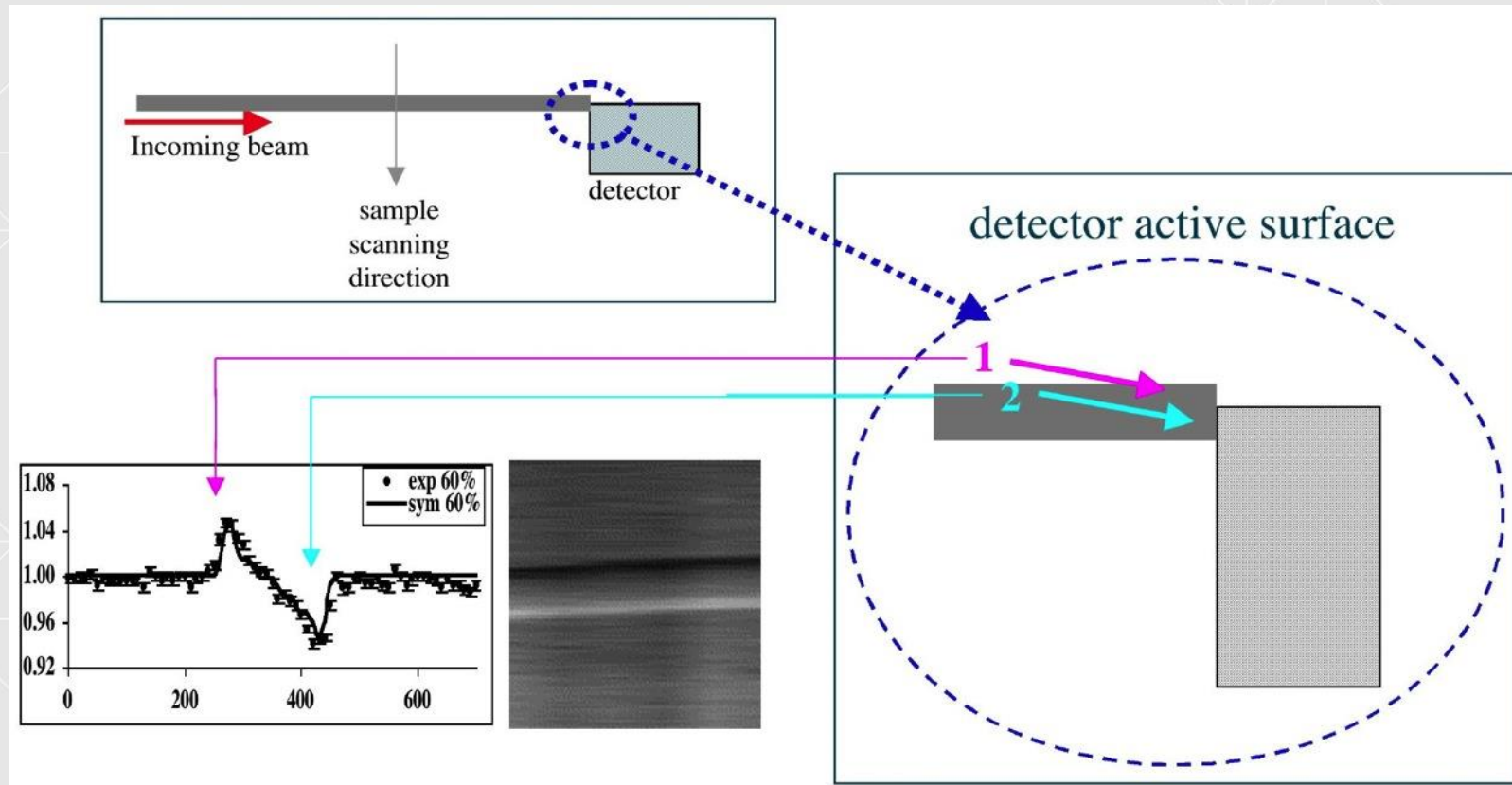
a small misalignment makes it more sensitive:



NOTE: NO ABSORPTION

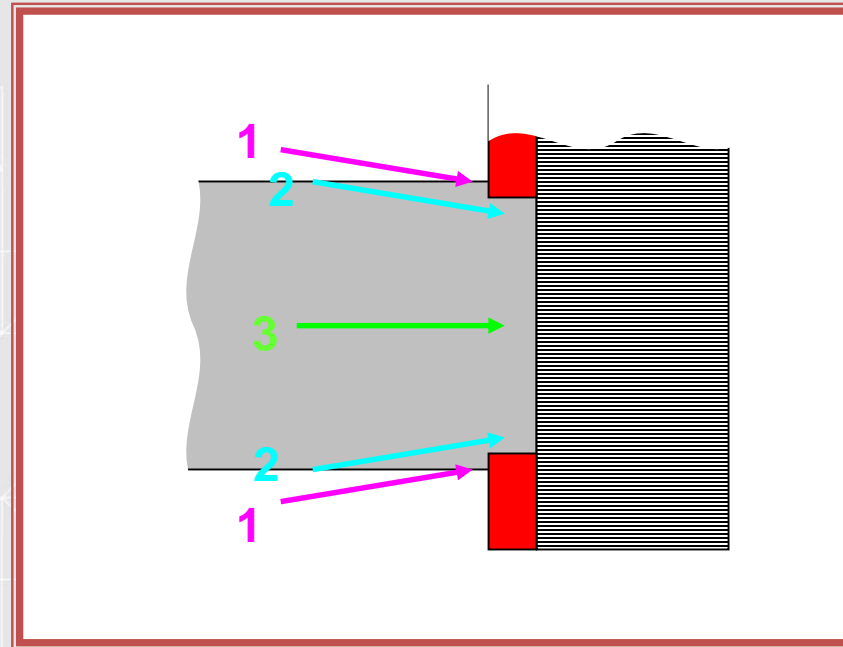
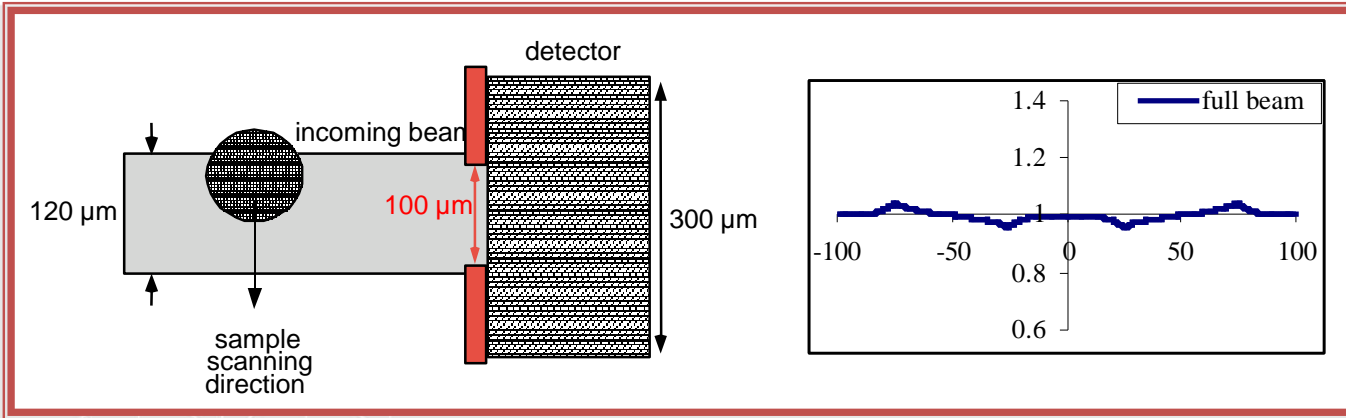
acquired image (fibre)

A different way to obtain a similar effect: The Edge Illumination Technique

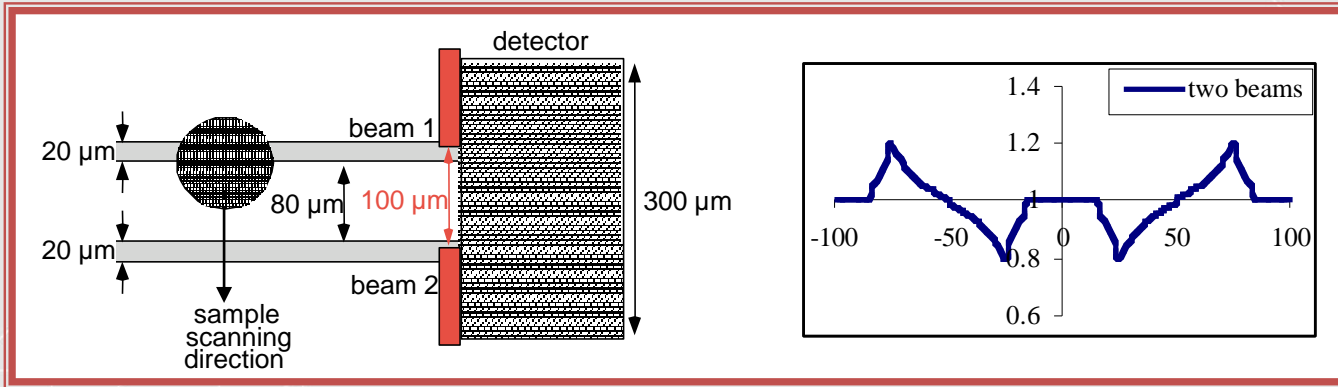


Provides results similar to ABI but opens the way to the use of **divergent** and **polychromatic** beams

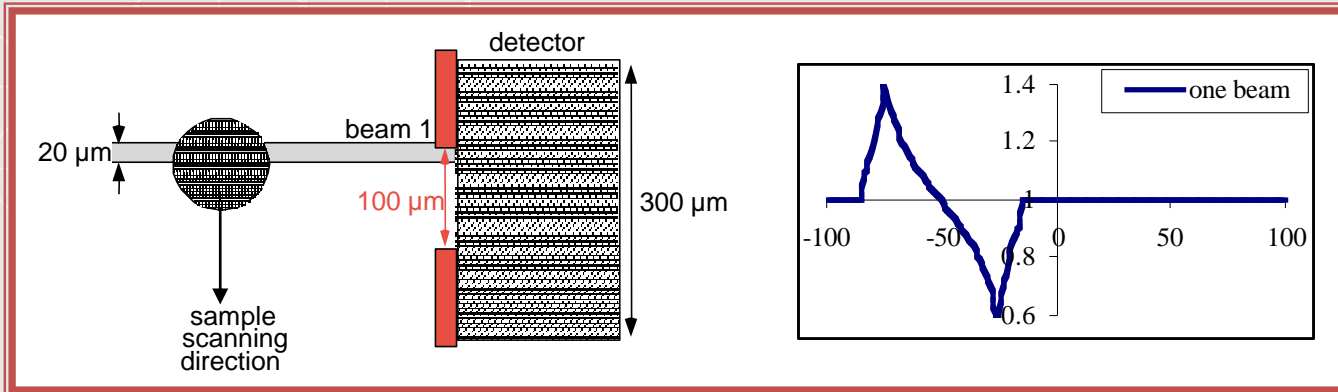
How did the idea come about? (1)



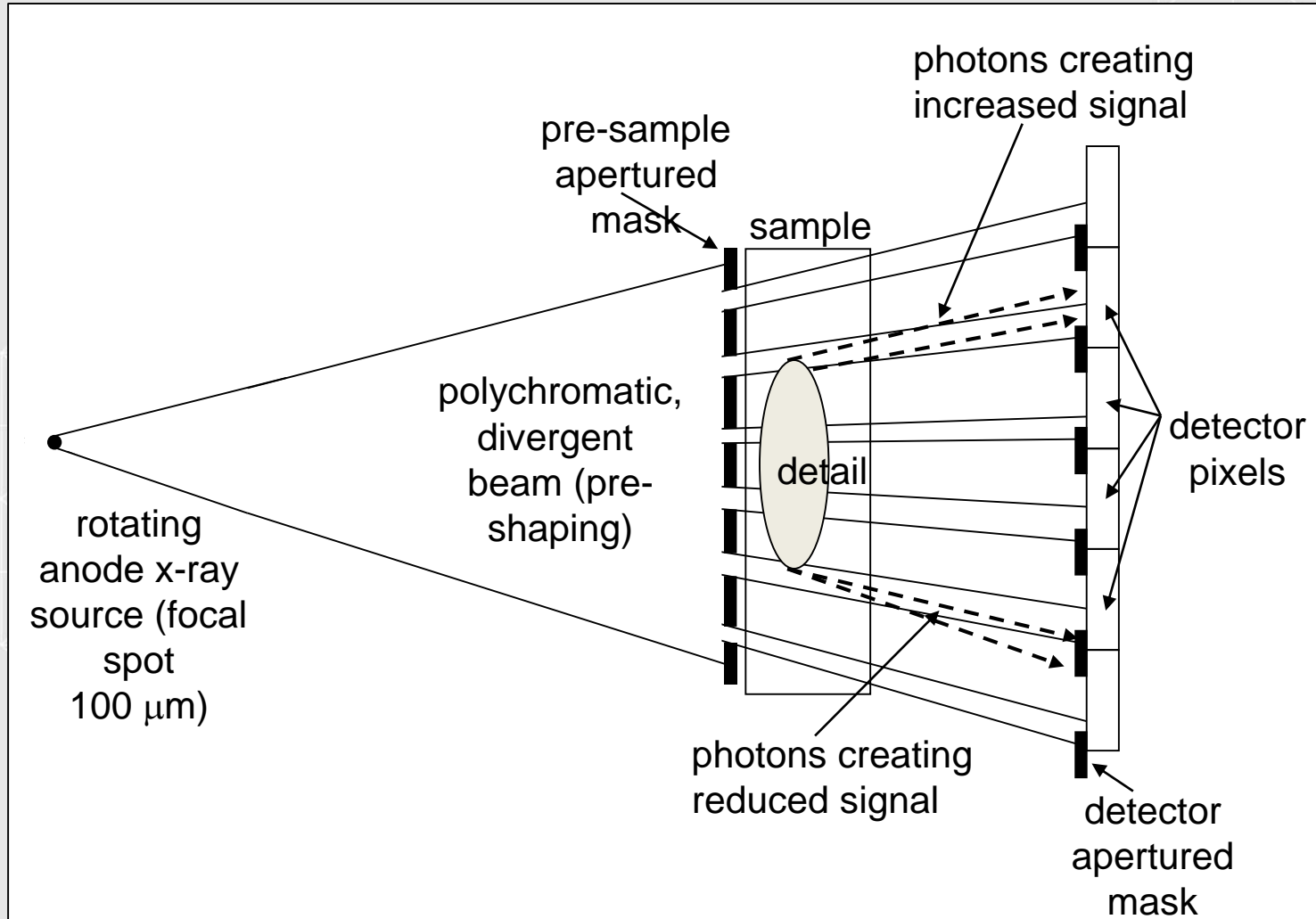
How did the idea come about? (2)



PLUS you become independent from the pixel size!

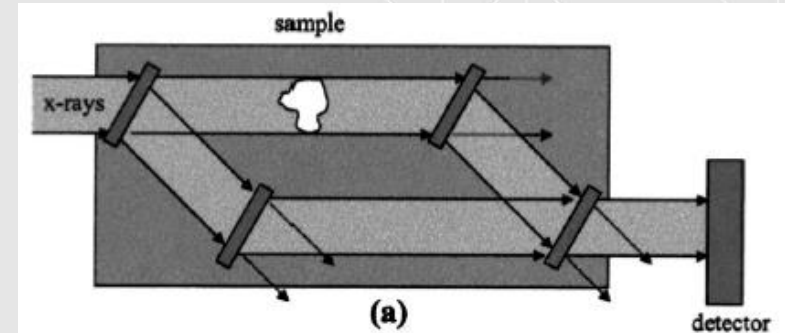
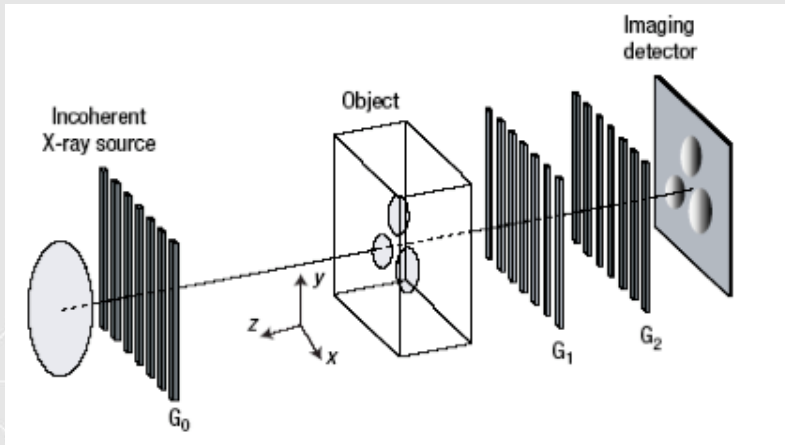


THE METHOD CAN BE ADAPTED TO A DIVERGENT AND POLYCHROMATIC (=conventional) SOURCE

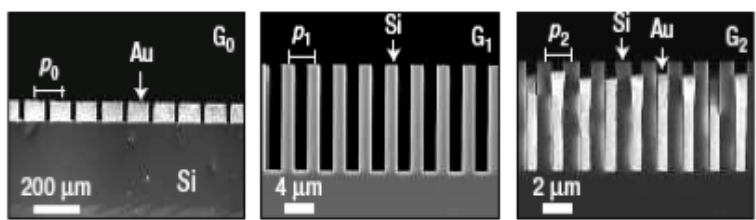


NB for those of you who are familiar with grating (or Talbot, or Talbot-Lau) interferometers **this isn't one!**

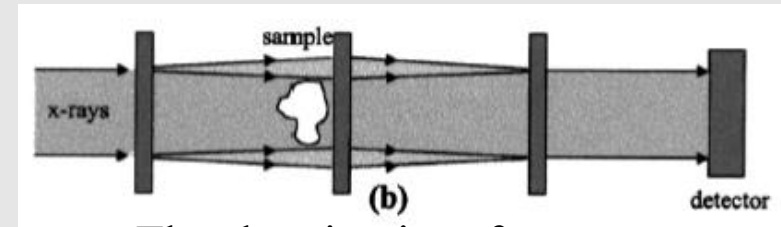
Interlude: the TALBOT/LAU interferometer: much smaller pitches, and based on a coherent effect



The classic, "Bonse-Hart" interferometer

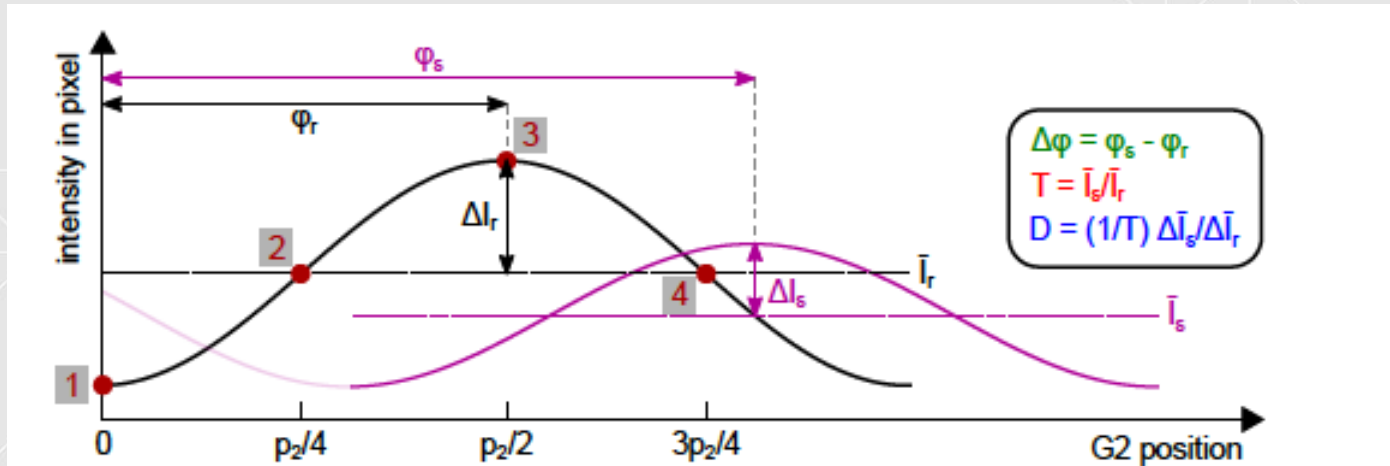


The used gratings, obtained through microfabrication techniques

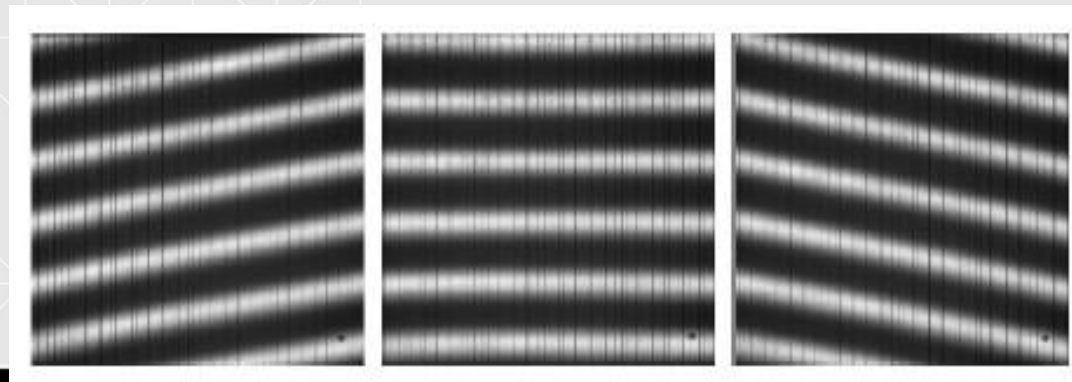


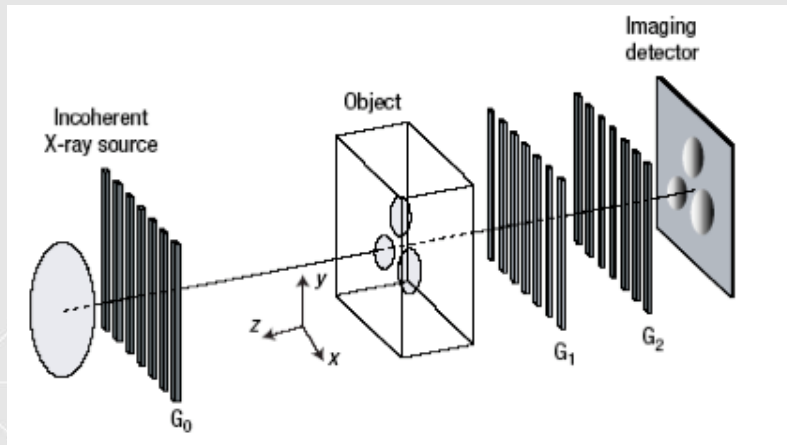
The shearing interferometer

1. Phase stepping

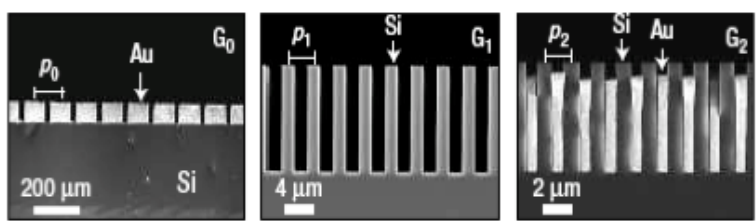


2. Moirè fringes





- increased exposure times (source grating covering most of the source, silicon substrates, limited angular acceptance)
- chromaticity (reduced fringe visibility away from design energy)
- the sensitivity to environmental vibrations (itches of a few μm -> required tolerance pitch/10 (Weitkamp *et al*, 2005), plus phase stepping -> tens of nm (!) (Zambelli *et al*, 2010))
- inefficient dose delivery: detector grating -> 50% fill-factor, + absorption in Si (40% through 1x300 μm wafer, 60% through 2 wafers, and normally wafers are THICKER)
- the field of view is currently limited to $\sim 6 \times 6 \text{ cm}^2$



The used gratings, obtained through microfabrication techniques



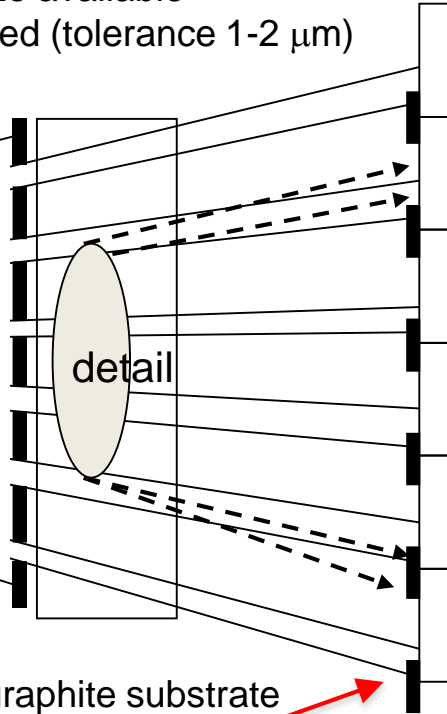
THE METHOD CAN BE ADAPTED TO A DIVERGENT AND POLYCHROMATIC (=conventional) SOURCE

- LARGE mask pitch (e.g. 50-200 μm)
- easy to fabricate
- large size available
- easy to keep aligned (tolerance 1-2 μm)

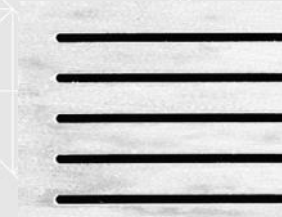
no source grating

Focal spot $\sim 100 \mu\text{m}$, plus full poly spectrum; coherence length at 1st mask $< 1 \mu\text{m}$, while pitch at least 100x larger \rightarrow **incoherence**

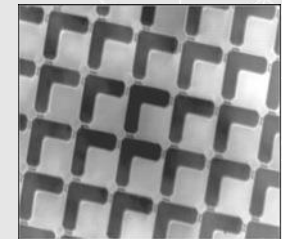
- on low-absorbing graphite substrate
- pre-sample, protects sample!
- only source of extra dose, can be kept to a small fraction! (even zero – see Olivo *et al* Med Phys 40 (2013) 090701)



Masks can be:

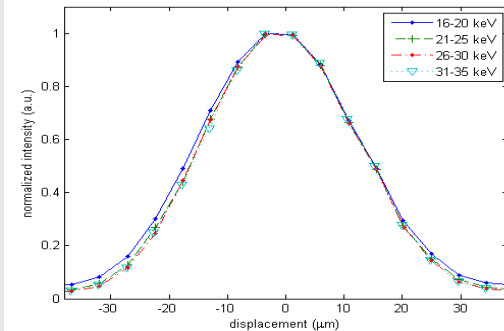


OR:



For 2D sensitivity (see Olivo *et al* APL 94 (2009) 044108)

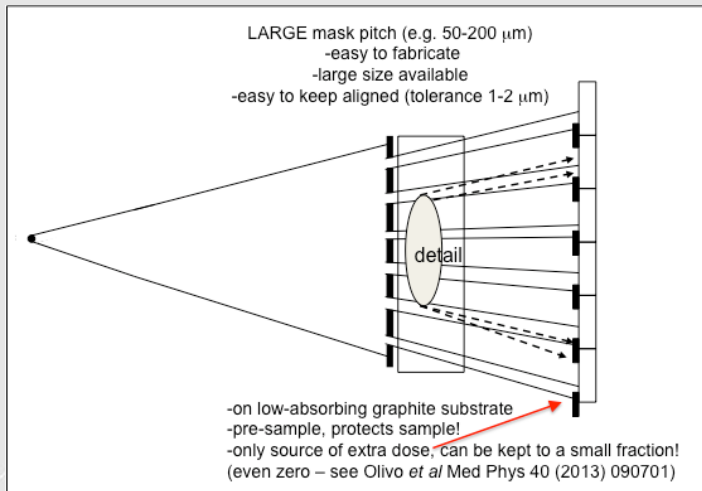
AND are fully achromatic



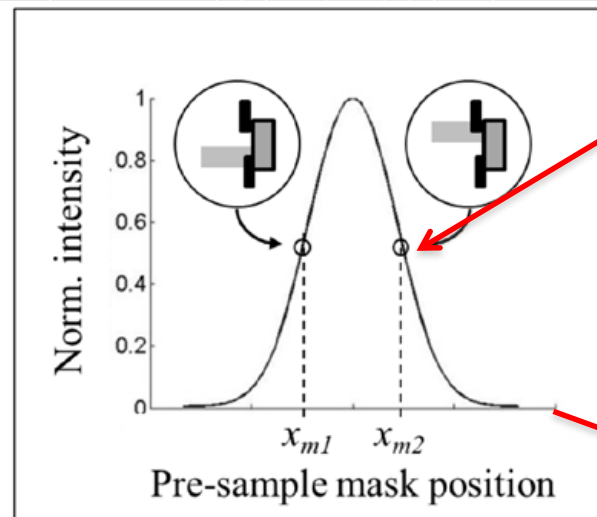
(Endrizzi *et al*, Opt Exp 23, 2015)



Compared to grating interferometry,  we use much larger periods, which has important consequences:



- 1) Beamlets do not overlap/interfere (NB they wouldn't anyway as beam not sufficiently coherent)
- 2) The mask period has **no influence whatsoever on the sensitivity** – only on the spatial resolution.
- 3) The sensitivity is an issue of the **individual beamlet**, in particular of the slopes of its shape.

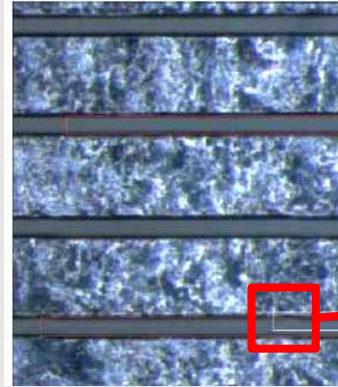


the aim of the mask is simply to repeat the EI condition multiple times in space

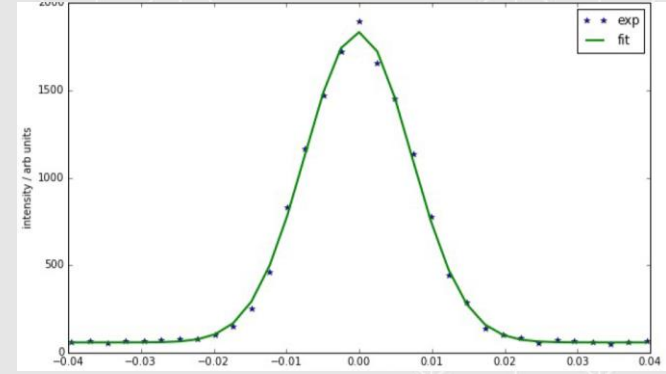
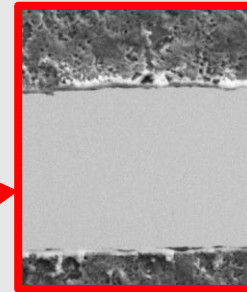
note also that typically we have extremely low

Other consequences of the “large” mask period:

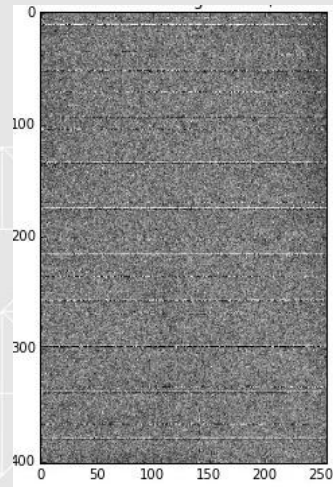
1) Large, substrate-less masks can be fabricated at very low cost by laser ablation on tungsten foil. Early tests show a) negligible offset and b) image quality comparable to that of masks obtained via lithography.



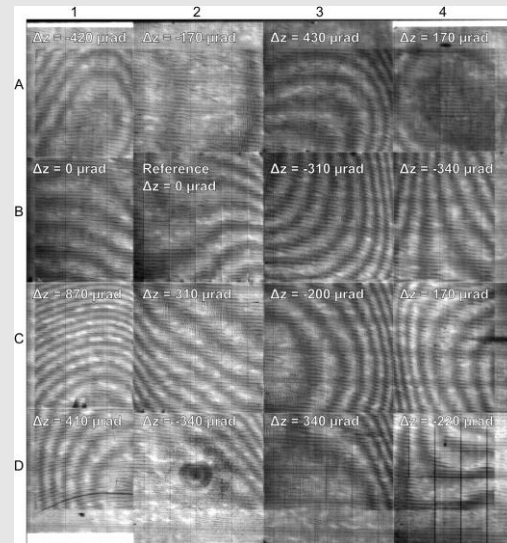
Courtesy K. Jefimovs & R. Brönnimann, EMPA



2) Whatever the fabrication method, flat fields are flat! This is what enables easy access to **single-shot** methods, as the same illumination level can be assumed throughout the field of view (more later).

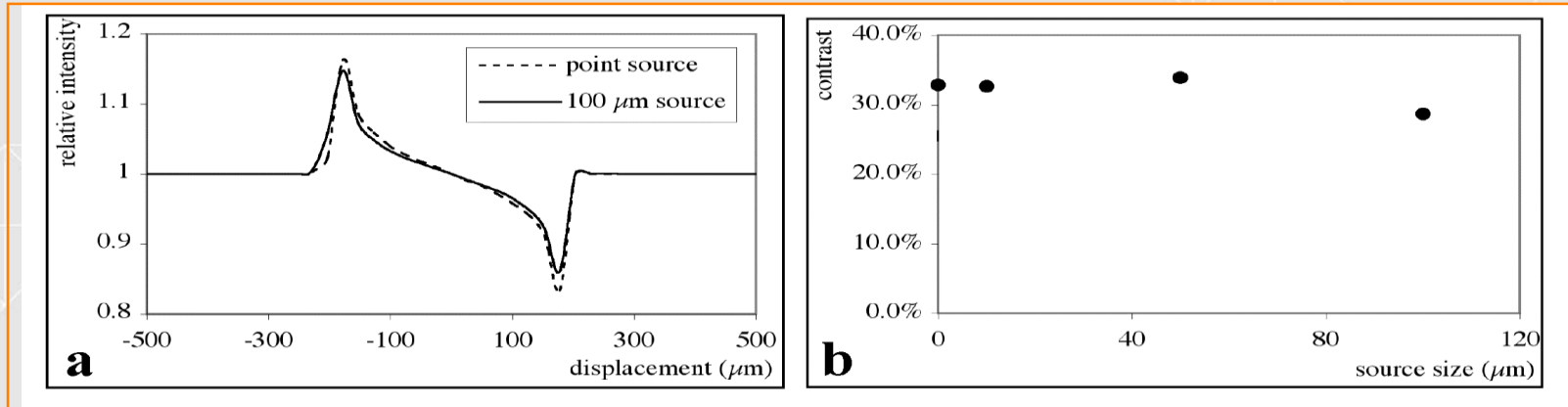


EI (non-tiled masks)



GI (tiled gratings)

Little loss of signal intensity for source sizes up to 100 μm

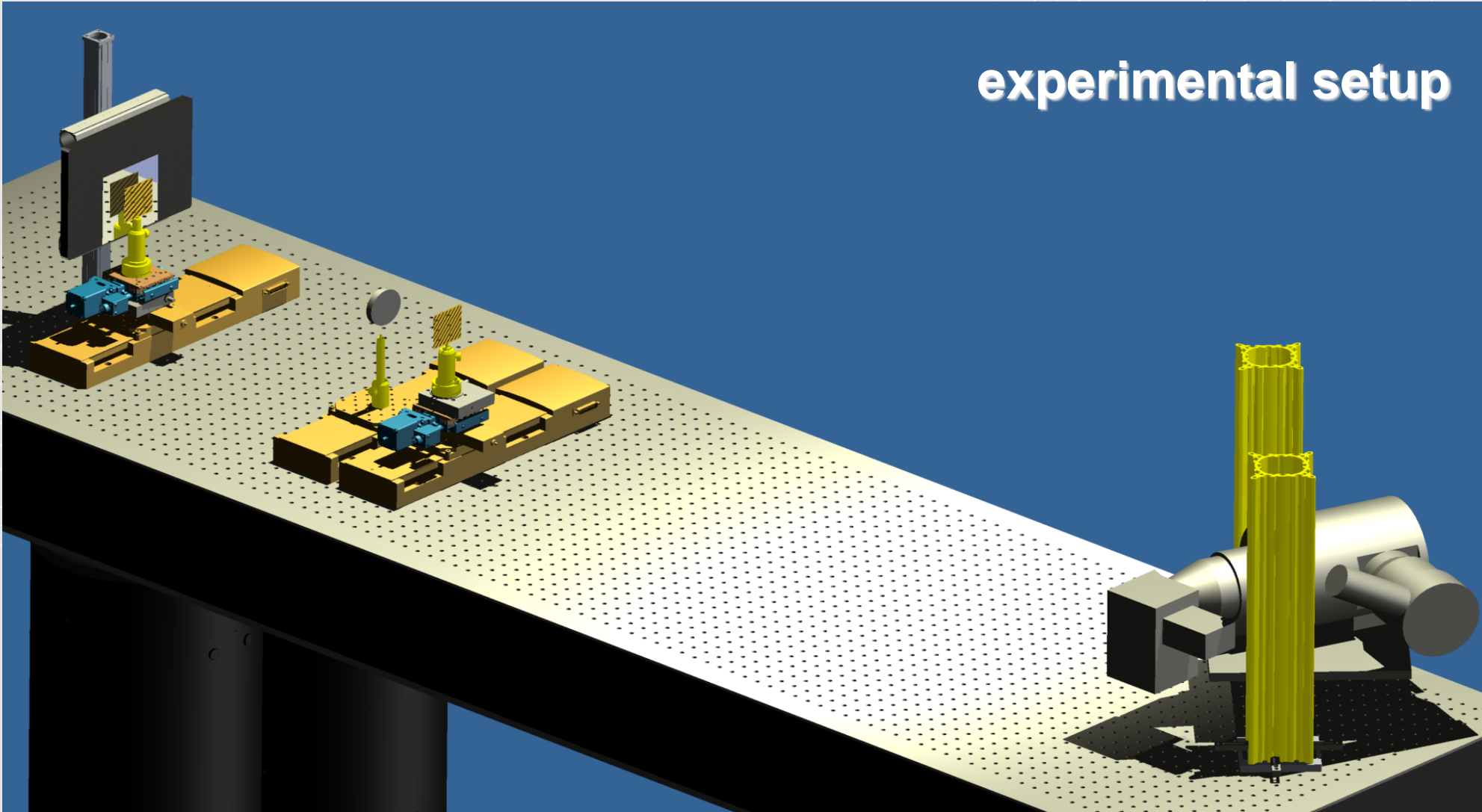


Which can be achieved with state-of-the-art mammo sources

Why?

- 1) Because we are only relying on refraction, which survives under relaxed coherence conditions;
- 2) Because we are use aperture pitches matching the pixel size, i.e. BIG: the projected source size remains $<$ pitch, and therefore blurring does “not” occur.

experimental setup





experimental setup



Preliminary results: the “us



RESEARCH HIGHLIGHTS

Selections from the
scientific literature

APPLIED PHYSICS

**Better X-ray
vision**

A new technique allows fainter features to be imaged by X-rays.

Conventional X-ray imaging relies on the absorption and scattering of X-ray photons by the object being imaged. But X-ray phase-contrast imaging instead detects changes in the photons' direction and velocity.

A. OLIVO ET AL.



Alessandro Olivo and his colleagues at University College London used a conventional X-ray source outfitted with grating masks — one in front of the object for imaging and one behind it. The masks were offset slightly from one another so that they filtered out some of the photons, reducing background noise. The detector measures by how much photons have deviated from their path, capturing different image data from conventional X-ray imaging and boosting the visibility of fine detail.

The team used its technique to image biological specimens such as a beetle (pictured), as well as samples of interest for medical imaging, materials science and security inspection. *Appl. Optics* 50, 1765–1769 (2011)

PHYSICS

Can You See Me Now?

A new x-ray technique may herald improved baggage screening and mammograms

X-rays can help reveal anything from bombs hidden in luggage to tumors in breasts, but some potentially vital clues might be too faint to capture with conventional methods. Now a new x-ray technique adapted from atom smashers could resolve more key details.

Conventional x-ray imaging works much like traditional photography, relying on the light—in this case, x-rays—that a target absorbs, transmits and scatters. To make out fine details, one typically needs a lot of x-rays, either over time, which can expose targets to damaging levels of radiation, or all at once from powerful sources such as circular particle accelerators, or synchrotrons, which are expensive.

Instead physicist Alessandro

Olivo of University College London and his colleagues suggest imaging an object by looking for very small deviations in an x-ray's direction as it moves through that object. Their idea is to take such x-ray phase-contrast imaging, which has been used in synchrotrons for more than 15 years, and use it with conventional x-rays.

The scientists rig conventional x-ray sources with gold gratings that are 100 microns or so thick—one in front of a target and one behind it. The holes on one grating do not line up exactly with the holes on the other, meaning x-rays that passed in straight lines through the first grating would get filtered out by the second, lowering background noise. The detector then analyzes only the

photons that deviated in direction as they passed through the object. This can lead to at least 10 times greater contrast than conventional imaging—"all details are more clearly visible, and details classically considered very hard to detect become detectable," Olivo says of findings reported recently in *Applied Optics*. Whereas bombs are usually visible in conventional x-ray imaging, they can be confused with other materials such as plastics or liquids. The scientists are now pushing imaging sensitivity even further with new gating designs and are working on 3-D scanning techniques by coming at the target from multiple angles.

This system can generate images in just seconds, far quicker than other x-ray phase-contrast techniques, which cannot exert as much power during scanning and thus require minutes, says radiation physicist David Bradley of the University of Surrey in England, who did not take part in this study. But it remains unclear if this system could work fast enough for security screening, says materials scientist Philip Withers of the University of Manchester in England. Withers does think the technology could lead to better medical imaging, as well as improvements in detecting defects in materials used in aerospace work.

—Charles Q. Choi



Olivo's x-ray of a chive plant



UCL

SPECIAL ISSUE

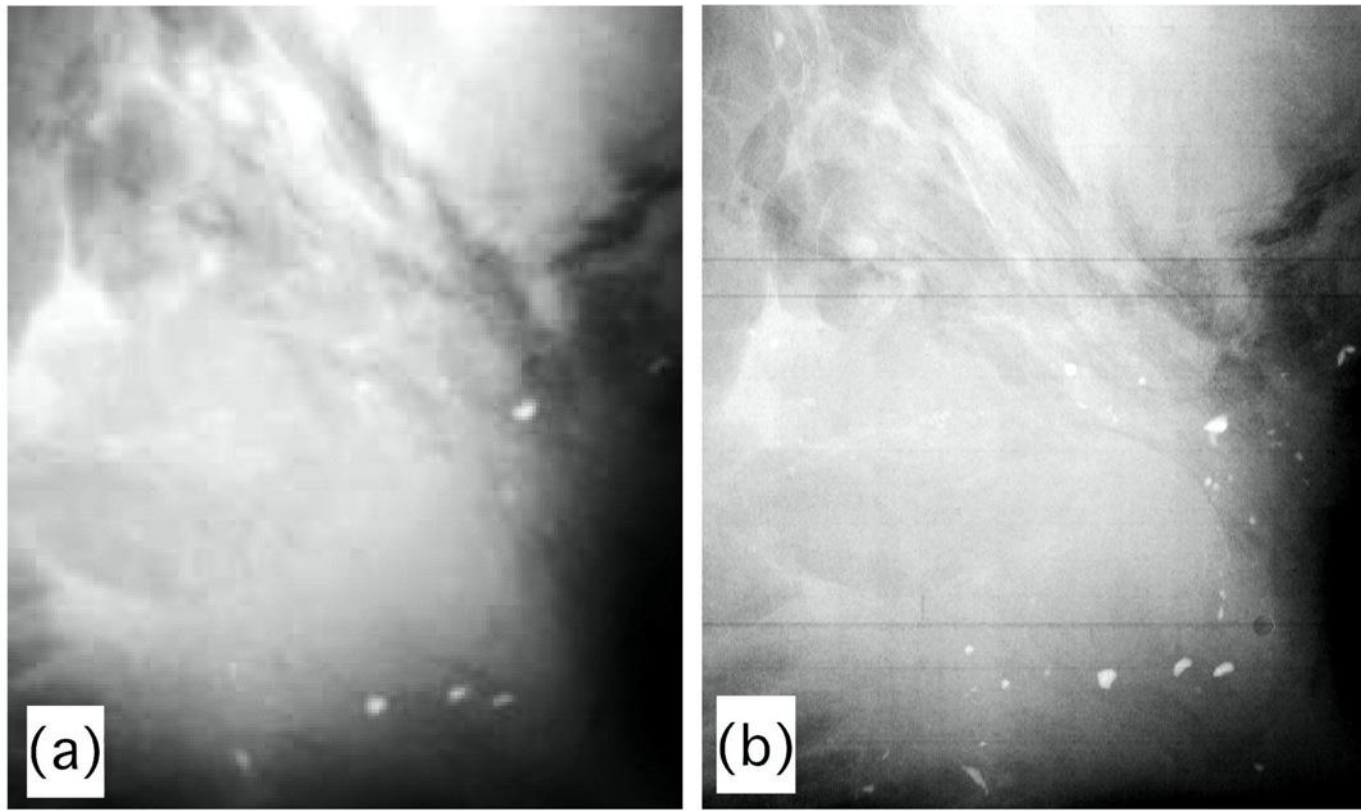
SCIENTIFIC AMERICAN

September 2011





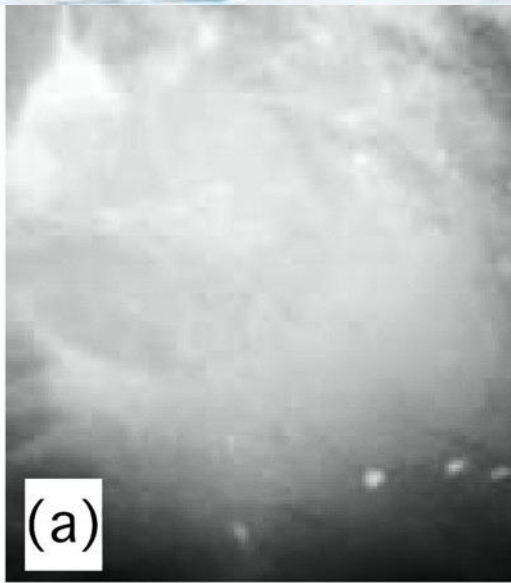
Preliminary results - mammo



(a): GE senographe Essential ADS 54.11; 25 kVp, 26 mAs

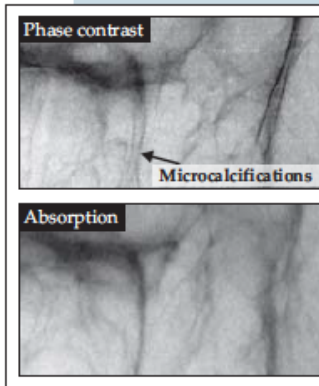
(b): coded-aperture XPCI, 40 kVp, 25 mA – **ENTRANCE** dose 7 mGy (< mammo!)

It has to be said the tissue was 2.5 cm thick -> we expect ~ same dose for thicker tissues



(a): GE senographe Essential AD
 (b): coded-aperture XPCi, 40 kVp
It has to be said the tissue was 2.5 cm th

Low-dose phase-contrast mammography. Small, treatable tumors are difficult to spot in mammograms because healthy and cancerous tissues differ little in how they absorb x rays. But absorption isn't the only source of contrast. As x rays pass through an inhomogeneous medium, they can acquire differences in phase—even if the medium is a uniform absorber. Early attempts at phase-contrast imaging required a synchrotron or other bright, coherent source of x rays. Now



Alessandro Olivo of University College London and his collaborators have built a prototype machine that performs phase-contrast mammography with a conventional x-ray tube at clinically acceptable doses. The setup works by masking the x-ray source with an array of hundreds of narrow, closely spaced holes. Each beam that emerges points at a single pixel of a flat-panel detector. The detector is also masked—such that half the x rays from each beam are prevented

from reaching their designated pixel. When an object is placed between the source and the detector, the beams suffer either absorption or, thanks to a change in phase, refraction. Because of the setup's geometry and the small angles of refraction involved, some refracted photons will still reach their pixel, but others will miss and hit the mask. Enough photons are diverted to the mask that they boost the contrast of what would otherwise be a conventional absorption image. Olivo's team tested its setup on donated samples of cancerous breast tissue. Microcalcifications that presage cancer showed up more clearly in the phase-contrast image than in an absorption image.

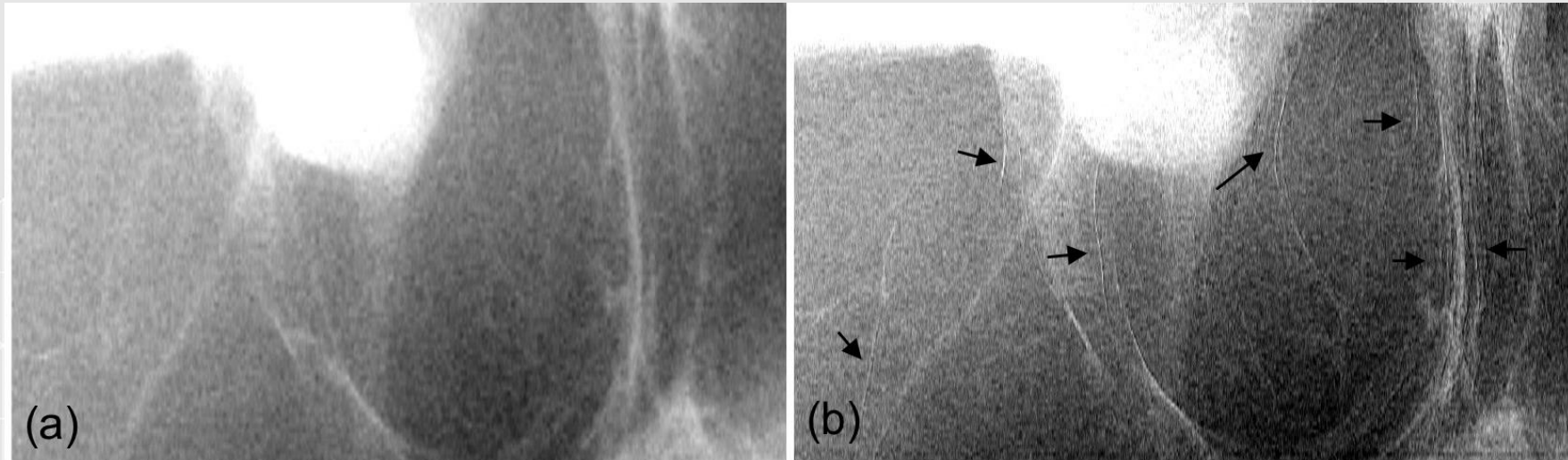
(A. Olivo et al., *Med. Phys.* **40**, 090701, 2013.) —CD

< mammo!)

S



Low dose mammo – thin tumour strands



(a): GE senographe Essential ADS 54.11; 25 kVp, 26 mAs

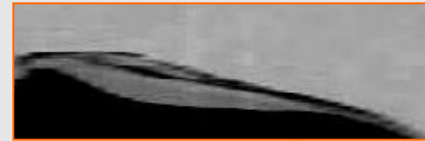
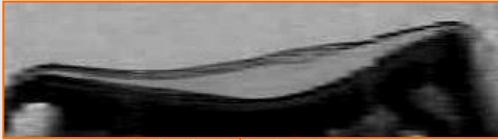
(b): lab-based EI XPCi, 40 kVp, 25 mA – entrance dose 7 mGy

Tissue 2 cm thick



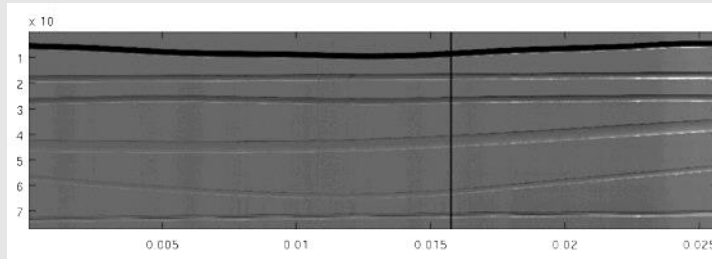
Preliminary results - cartilage imaging

Rat cartilage, $\sim 100 \mu\text{m}$ thick, invisible to conventional x-rays

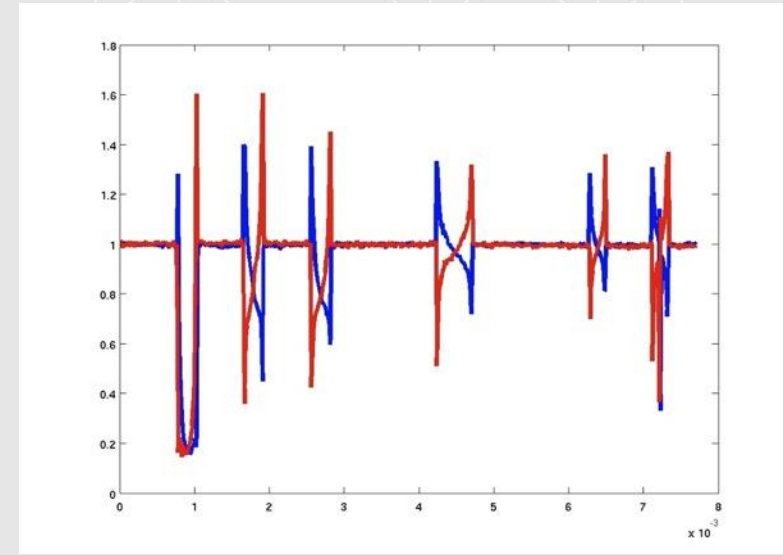
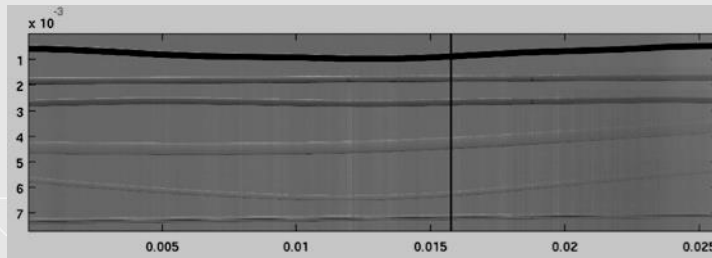


Quantitative phase contrast imaging

“SLOPE -”



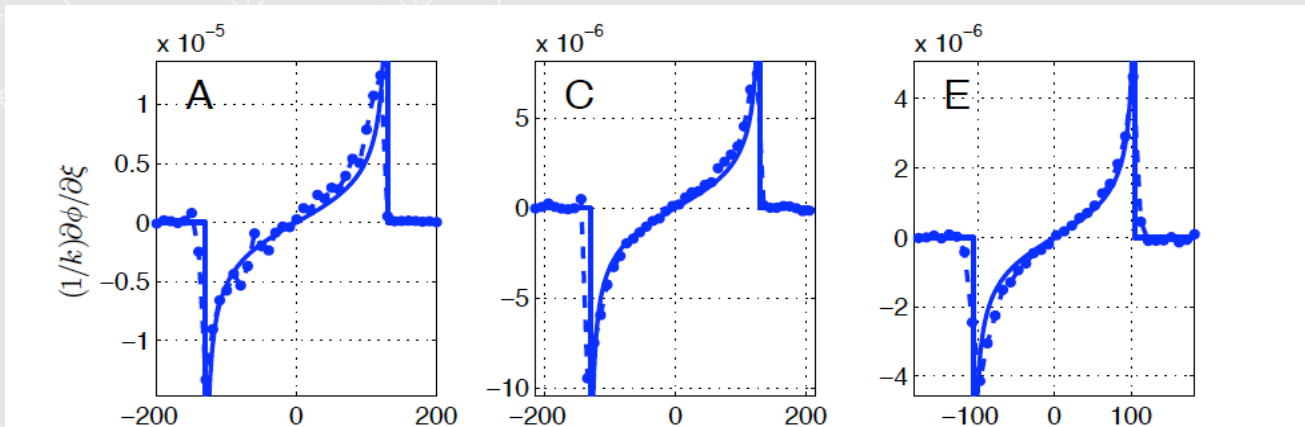
“SLOPE +”



Titanium

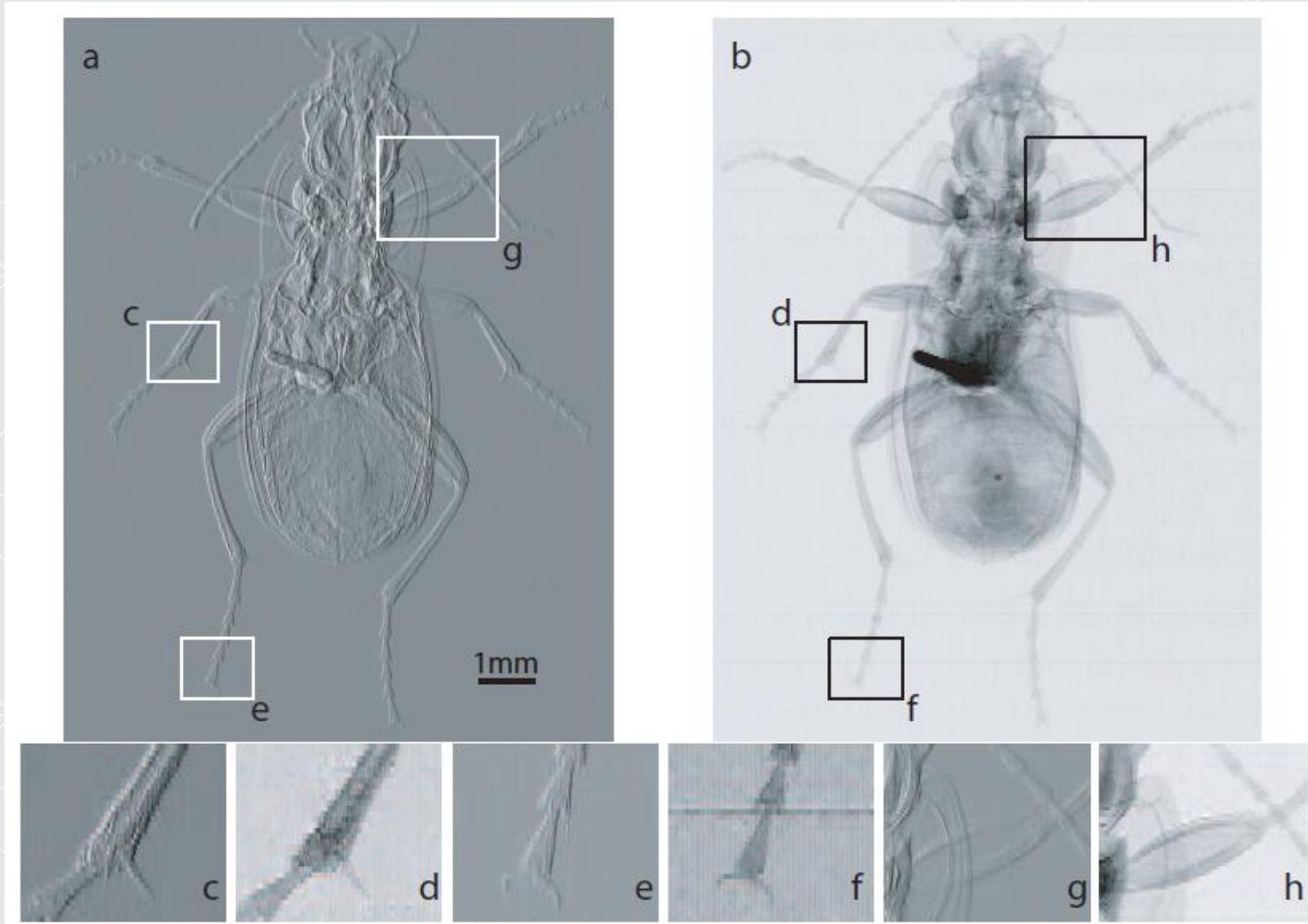
Aluminum

PEEK



Highly precise retrieval, for both high and low Z materials, up to high gradients where other methods break down

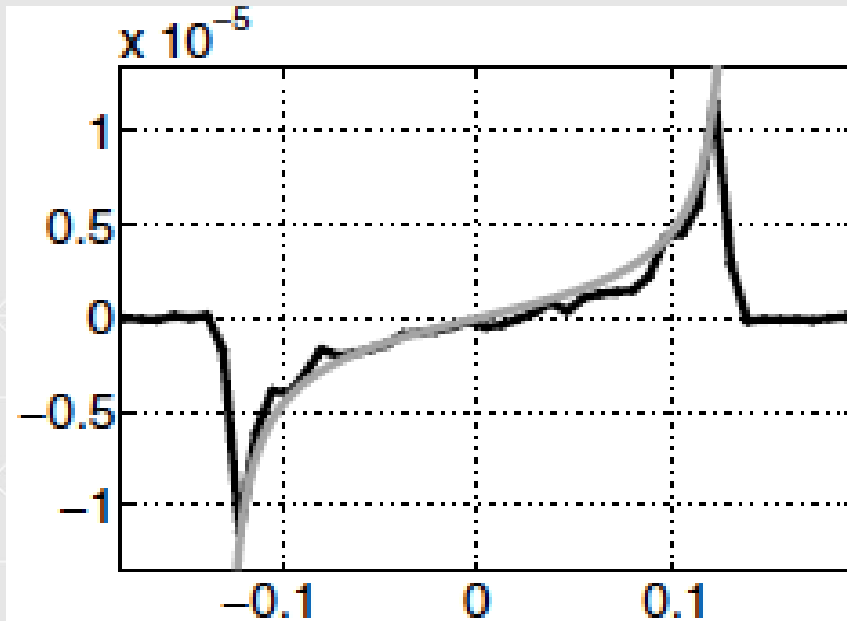
Quantitative phase contrast imaging



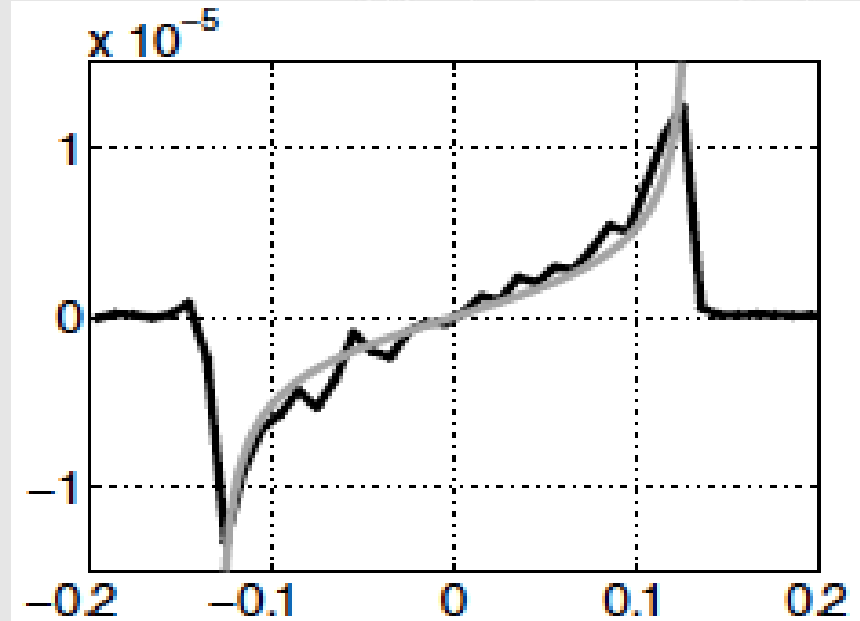
Phase retrieval with synchrotron and conventional sources:



Ti filament: retrieved @ synchrotron



and with conventional source!

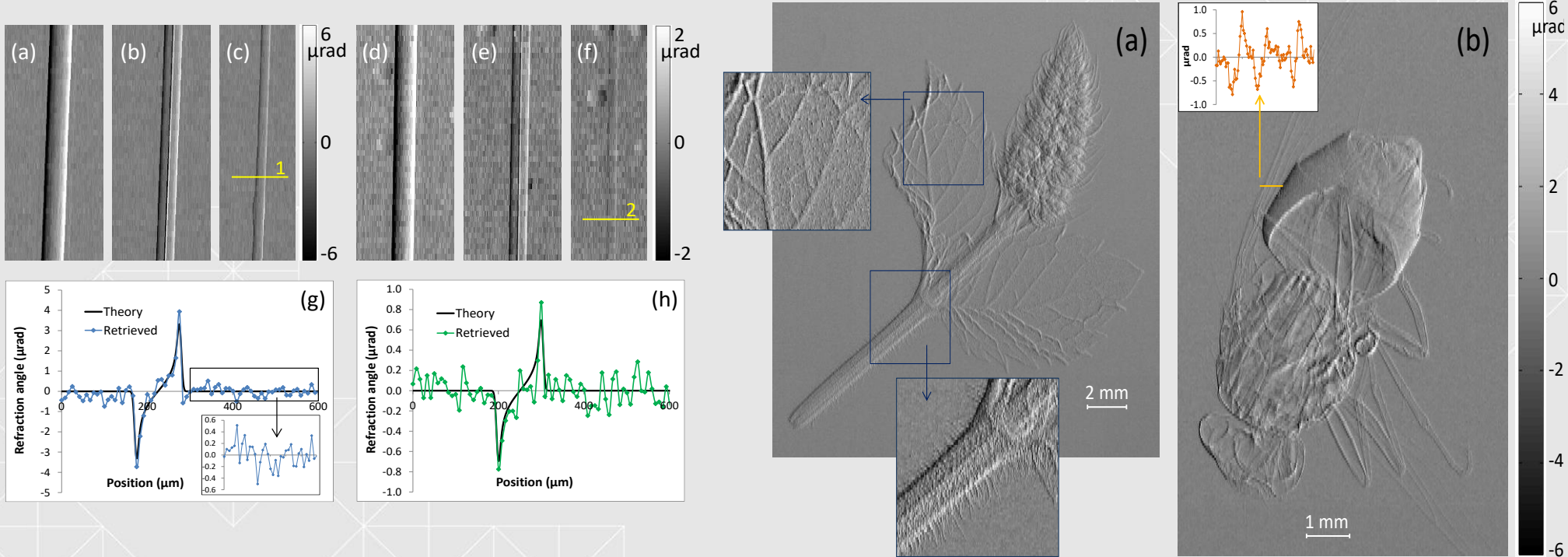


@ conventional source: incoherence modelled as beam spreading – the movement of the “spread” beam is then tracked and referred back to the phase shift that caused it.

But with lots of care as far as “effective energy” is concerned!

(See Munro & Olivo Phys. Rev. A **87** (2013) 053838)

More on the sensitivity of the lab system:



$$\Delta\theta_{x,eff} = \frac{1}{z_{od}} R^{-1} \left(\frac{I_{obj,+}}{I_{obj,-}} \right) \longrightarrow \sigma(\Delta\theta_{x,eff}); \frac{\sqrt{C(x_{e,+})}}{z_{od} \sqrt{2TI_0} [\rho_{ref,n}(x_{e,+}) - \rho_{ref,n}(x_{e,+} + d)]}$$

This gives a phase sensitivity of ~ 270 nRad, with only 2 images x 7s exposure each; same as reported by Thuring (Stampanoni's group) for GI. Revol reported a sensitivity of about 110 nRad but with 12 x 7s frames – as one can expect the value to scale with sqrt(exp time), that also fits.

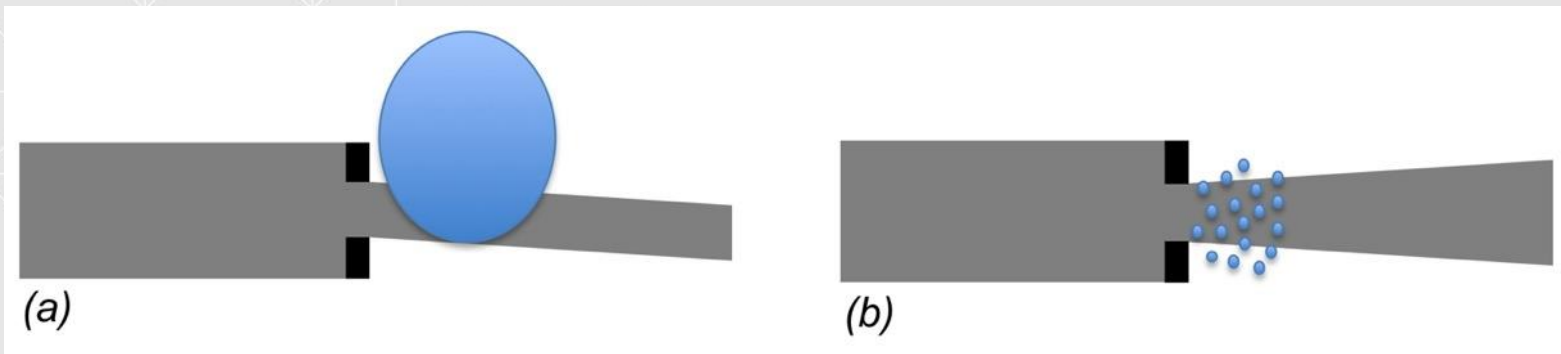
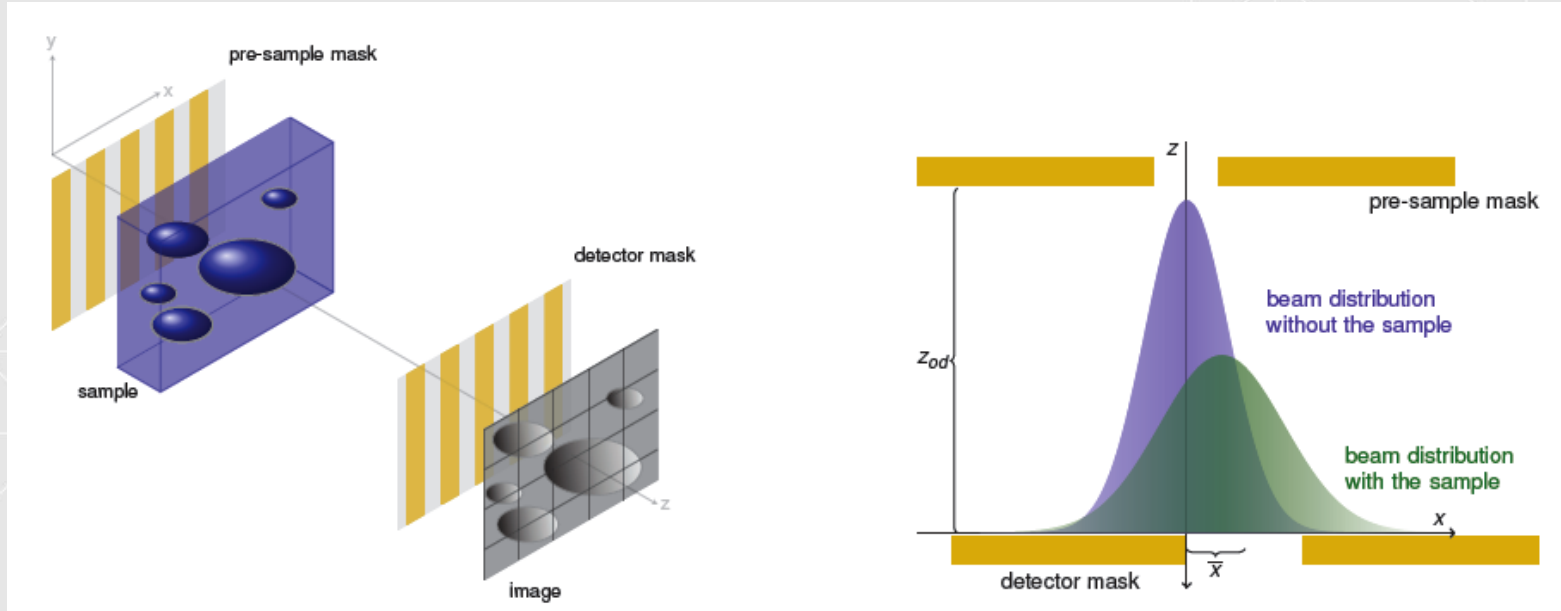
Following Munro's PNAS paper, other retrieval methods were developed:



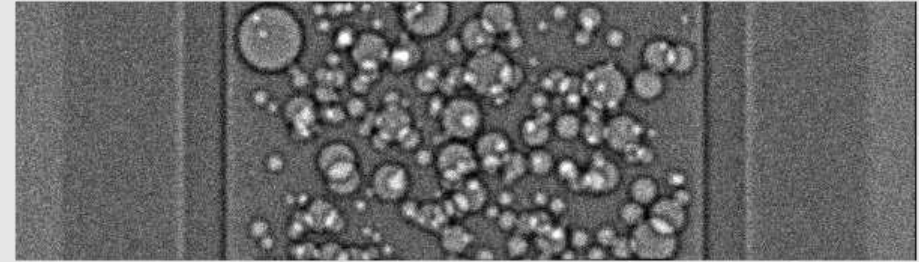
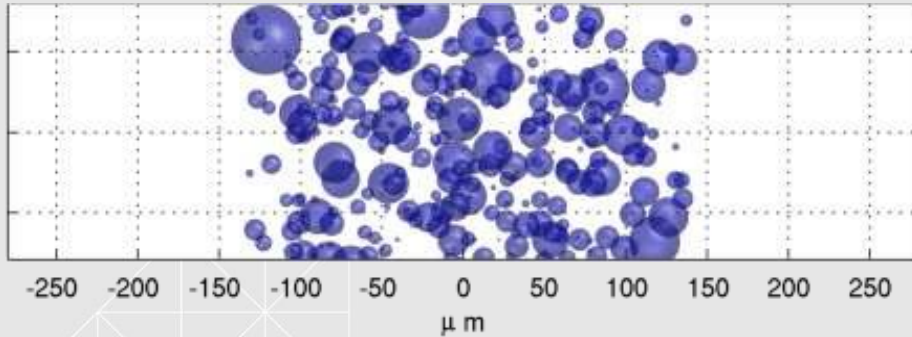
- 1) Inversion of the illumination curve (Munro et al Opt. Exp. **21** (2013) 11187; Diemoz et al Phys. Rev. Lett. **110** (2013) 138105): does not impose restricting conditions, simpler, requires experimental measurement of IC.
- 1) “Reverse Projections” (Hagen et al J. Phys. D: Appl. Phys. **49** (2016) 255501): CT only, exploits symmetry between projections acquired at angles θ and $\theta+180^\circ$ – inspired by work from Zhang and Zhu.
- 1) “Single Shot” (Diemoz et al J. Synchrotron Rad. **22** (2015) 1072): an adaptation to EI of Paganin's approach, requires simplifications but works reliably in many cases, recently adapted to lab setup allows ultra-fast phase CT acquisitions (minutes; Diemoz *et al* Phys. Rev. Appl. **7** (2017) 044029).



Three-shot DARK FIELD IMAGING retrieval

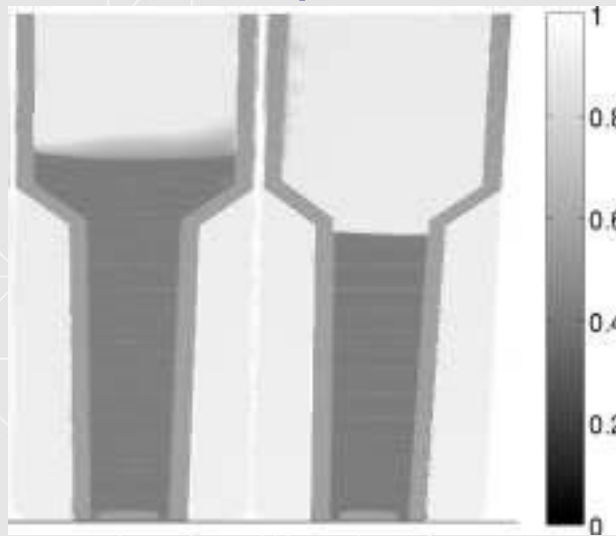


Microbubbles: a new concept of “phase-based” x-ray contrast agent



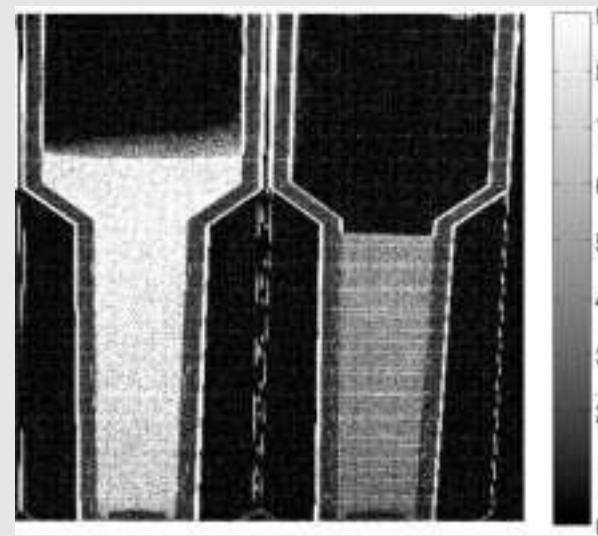
absorption

dark field



bubbles

no bubbles

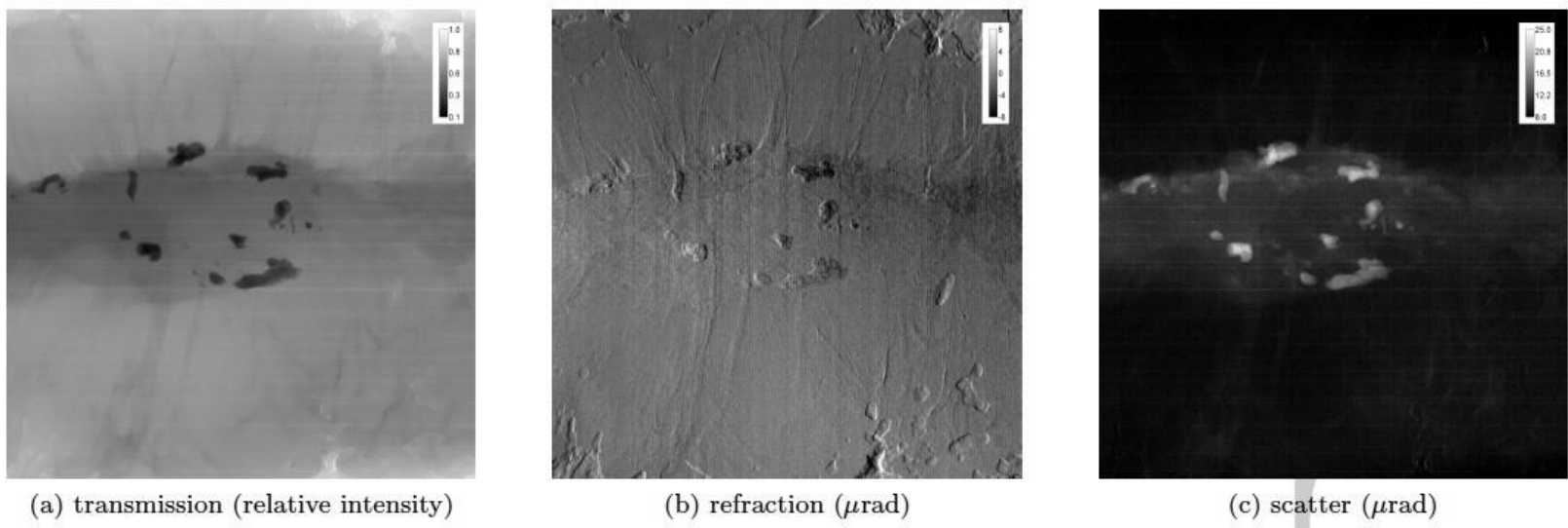


bubbles

no bubbles

DARK FIELD IMAGING of breast calcifications

3 images only, still within clinical dose limits!

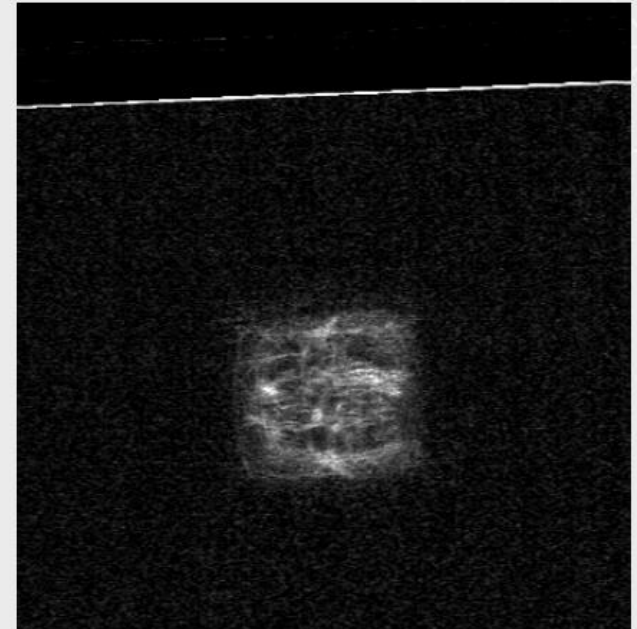
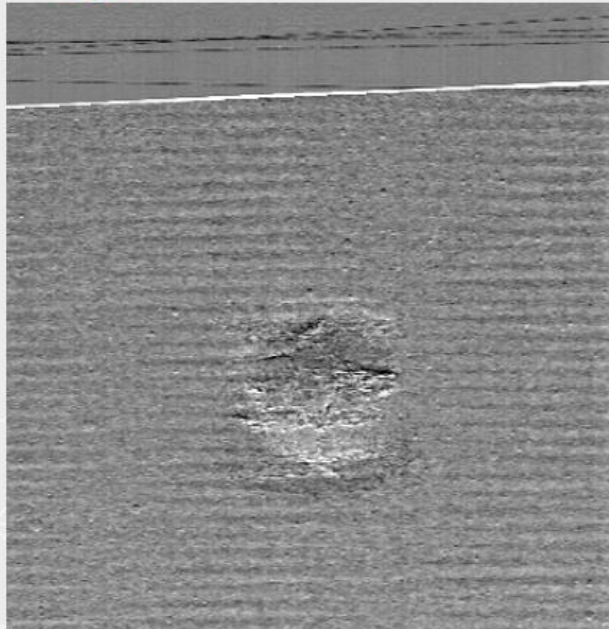
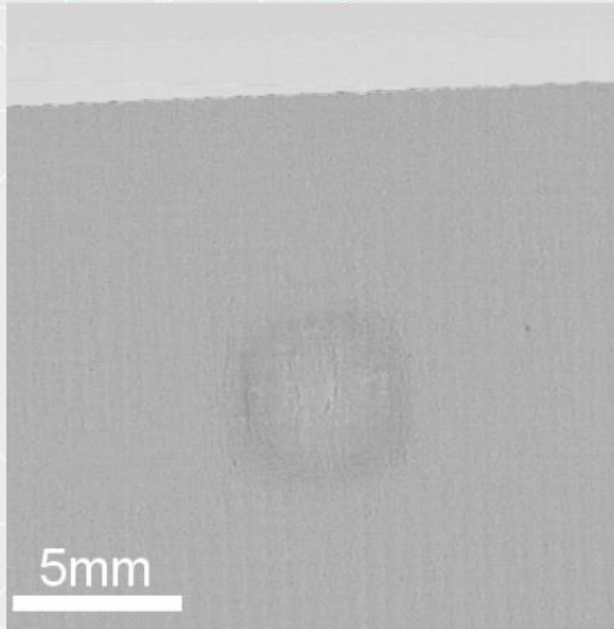


ENTRANCE dose 12 mGy (still compatible with mammo)

Non-medical applications: testing of composite materials/2



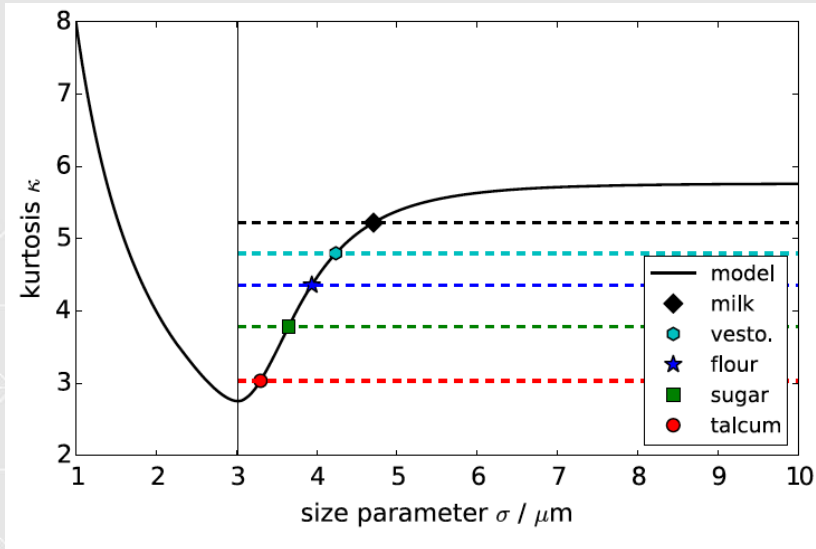
what's the shape of the damage?



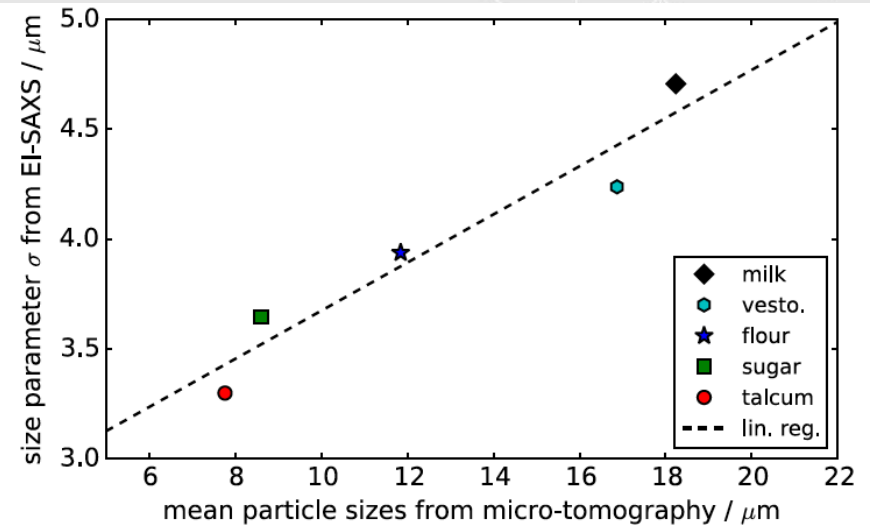


It can be made quantitative:

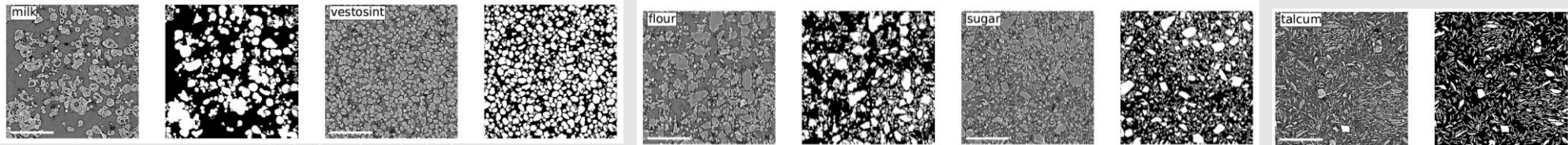
Theoretical curve fits experimental data;
inversion point depends on aperture size
-> can be selected in advance



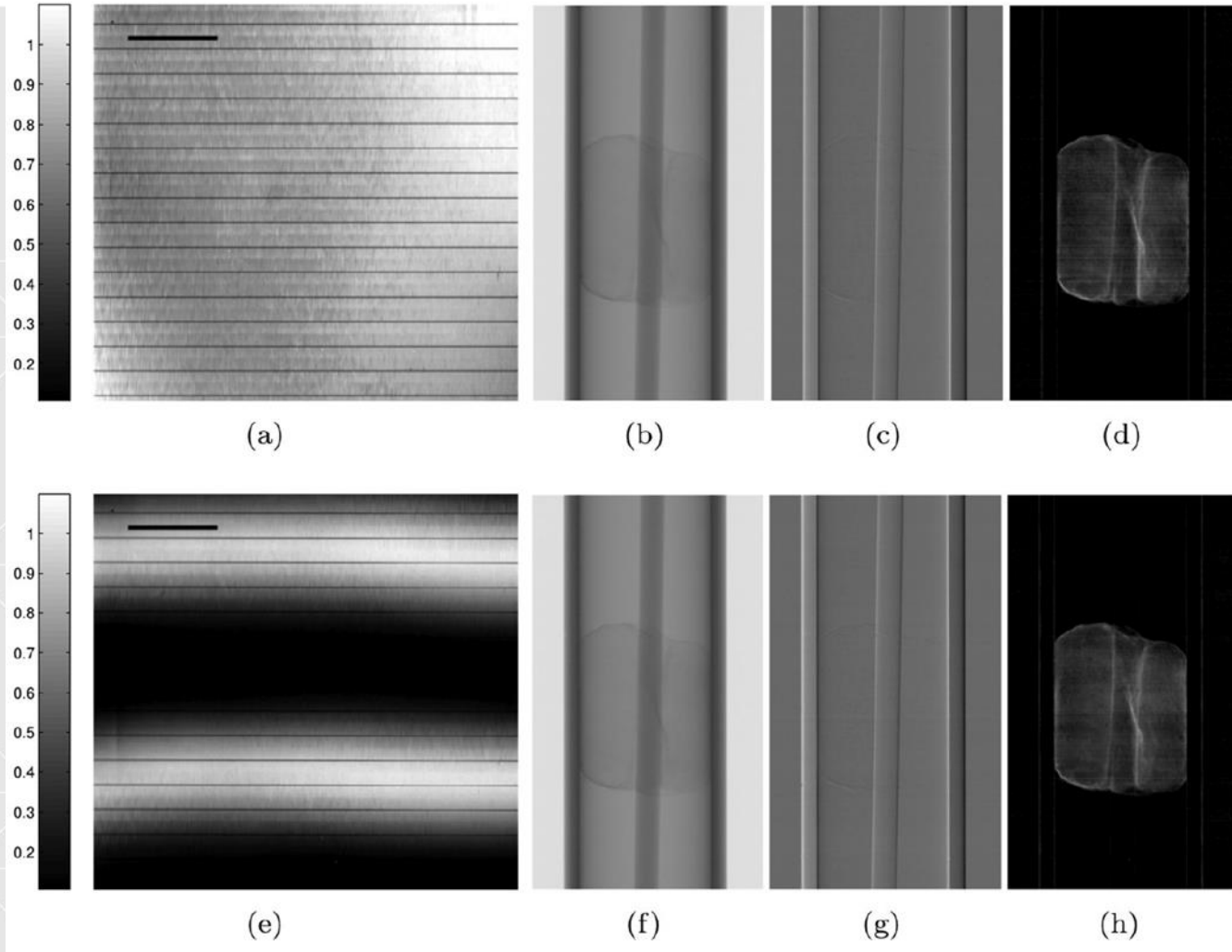
The experimentally validated model can be used to calibrate the system and extract size parameter directly from USAXS data



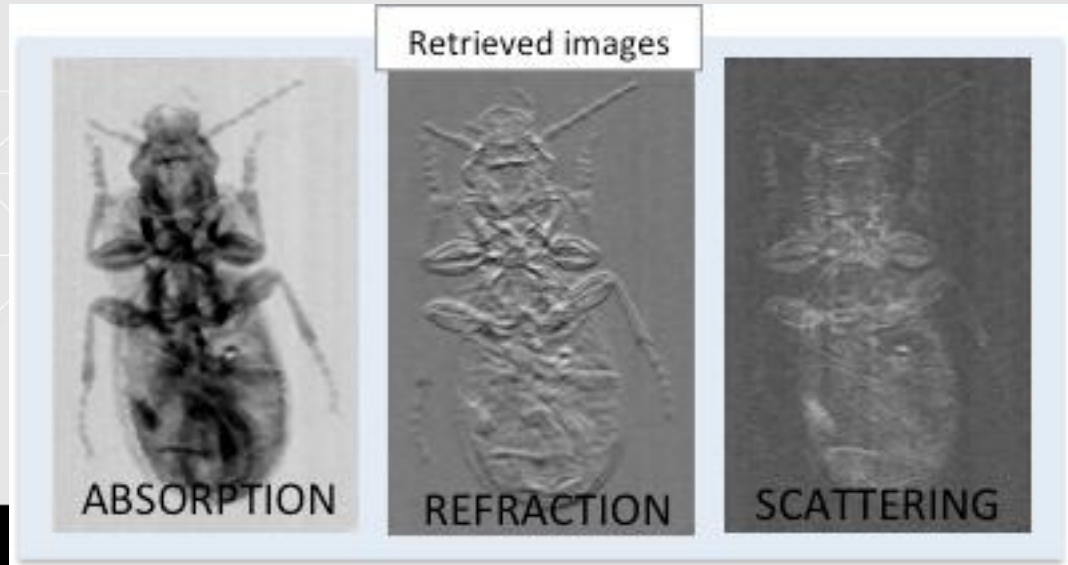
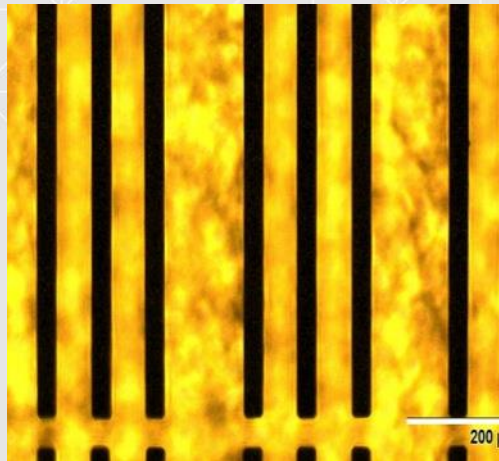
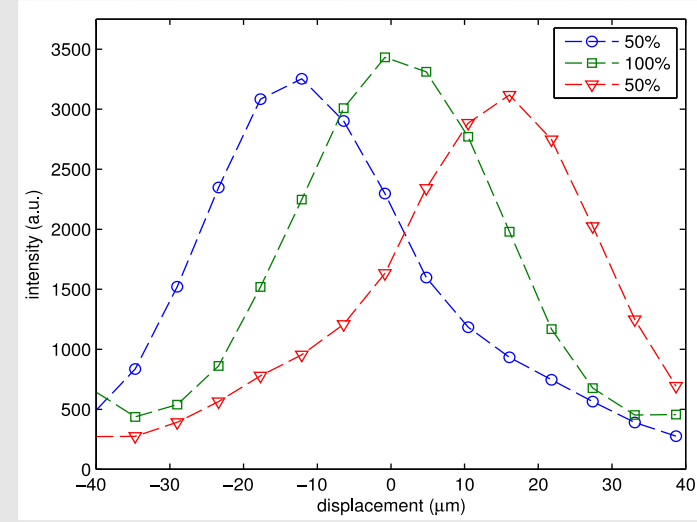
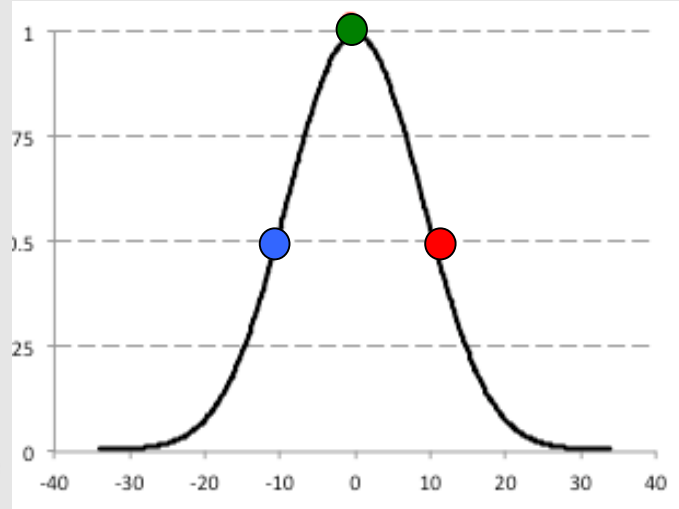
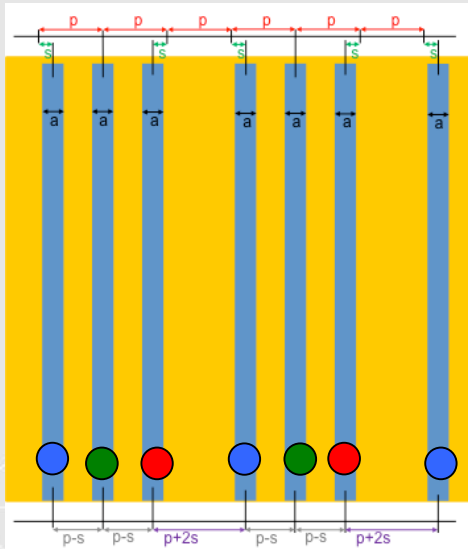
(validation obtained by segmenting nano-CT images of the powders and extracting average size)



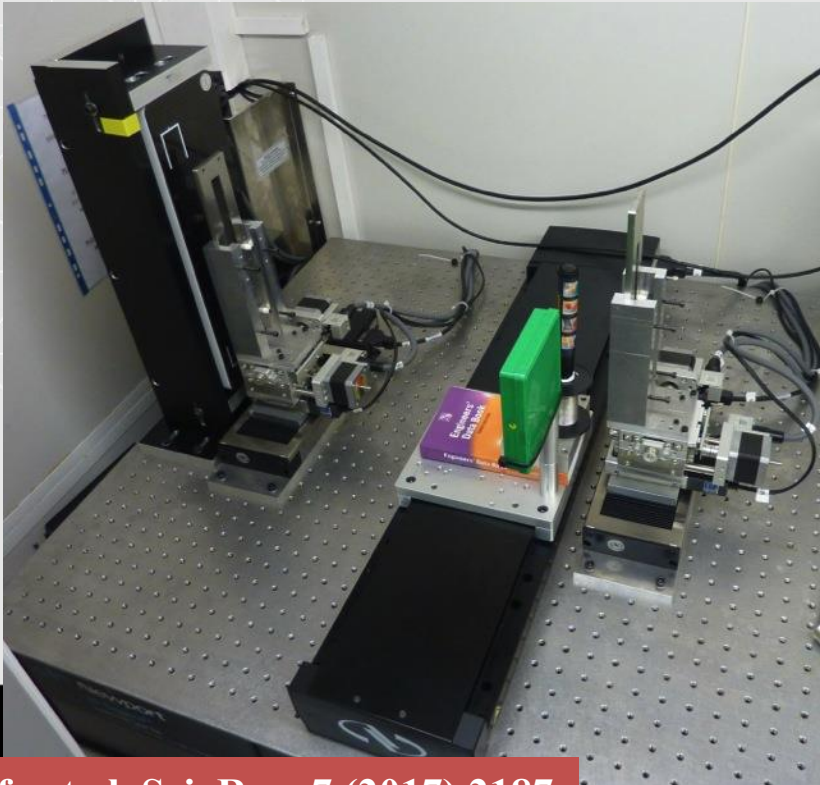
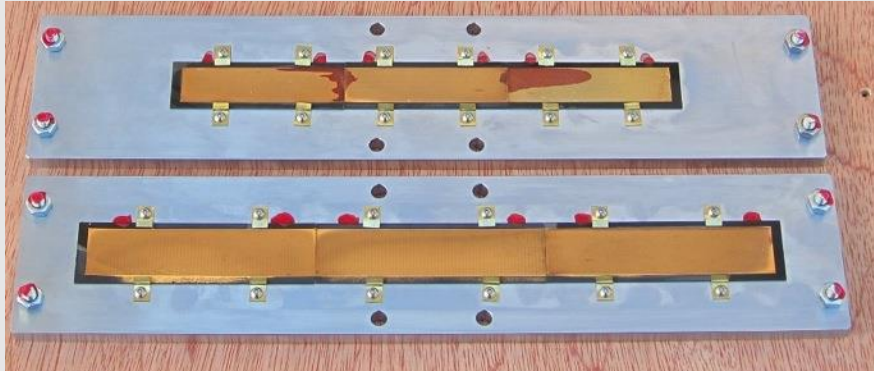
Importantly, the 3-image retrieval method removes the need to align the masks...



But you still need to displace the pre-sample mask at each step; in scanned acquisitions, use **ASYMMETRIC** masks!



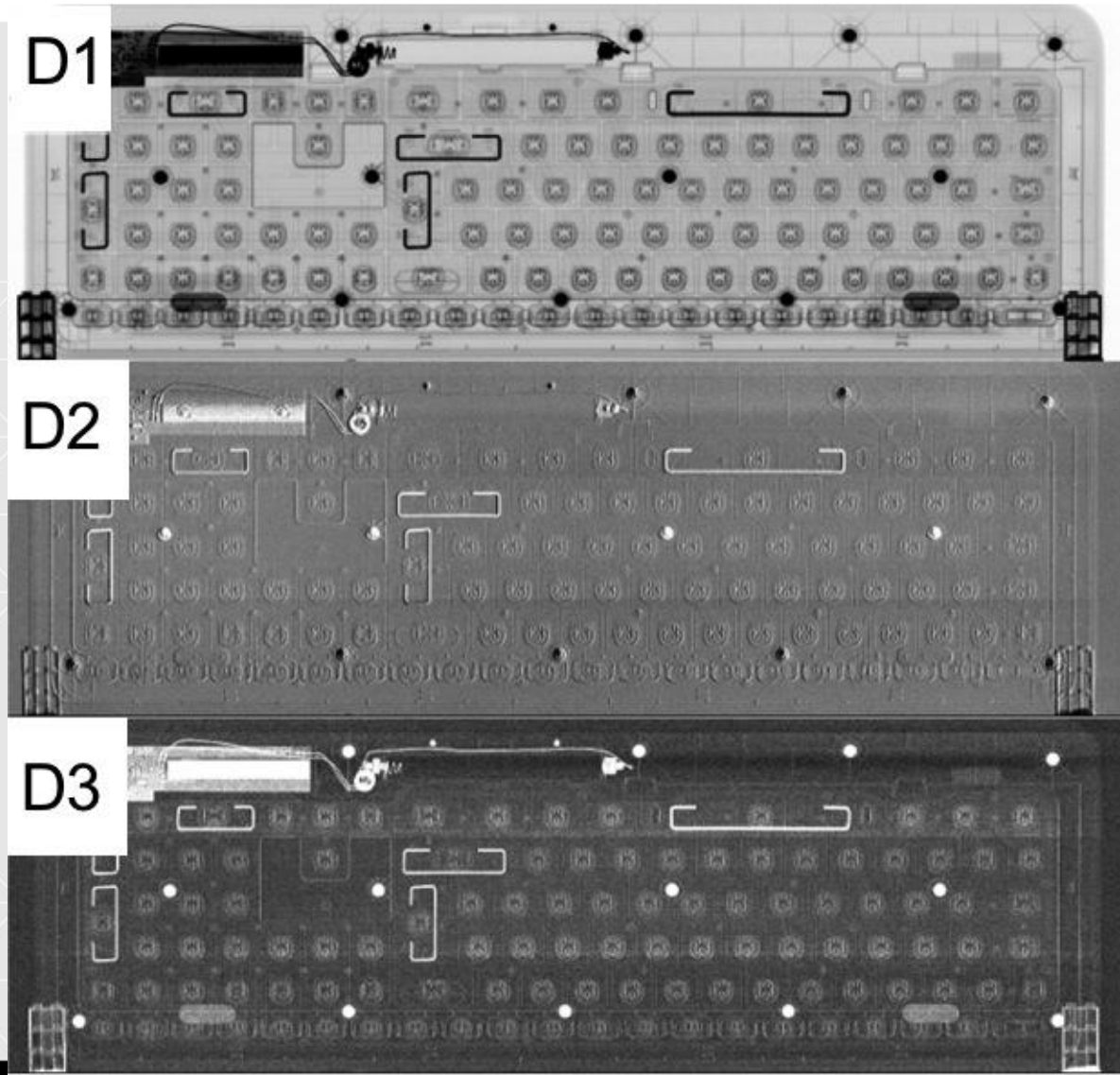
Used to build large FoV (20 x 50 cm²), high-energy pre-commercial prototype (results will be presented at IEEE 2016)



...but OK I'll show you a snippet...



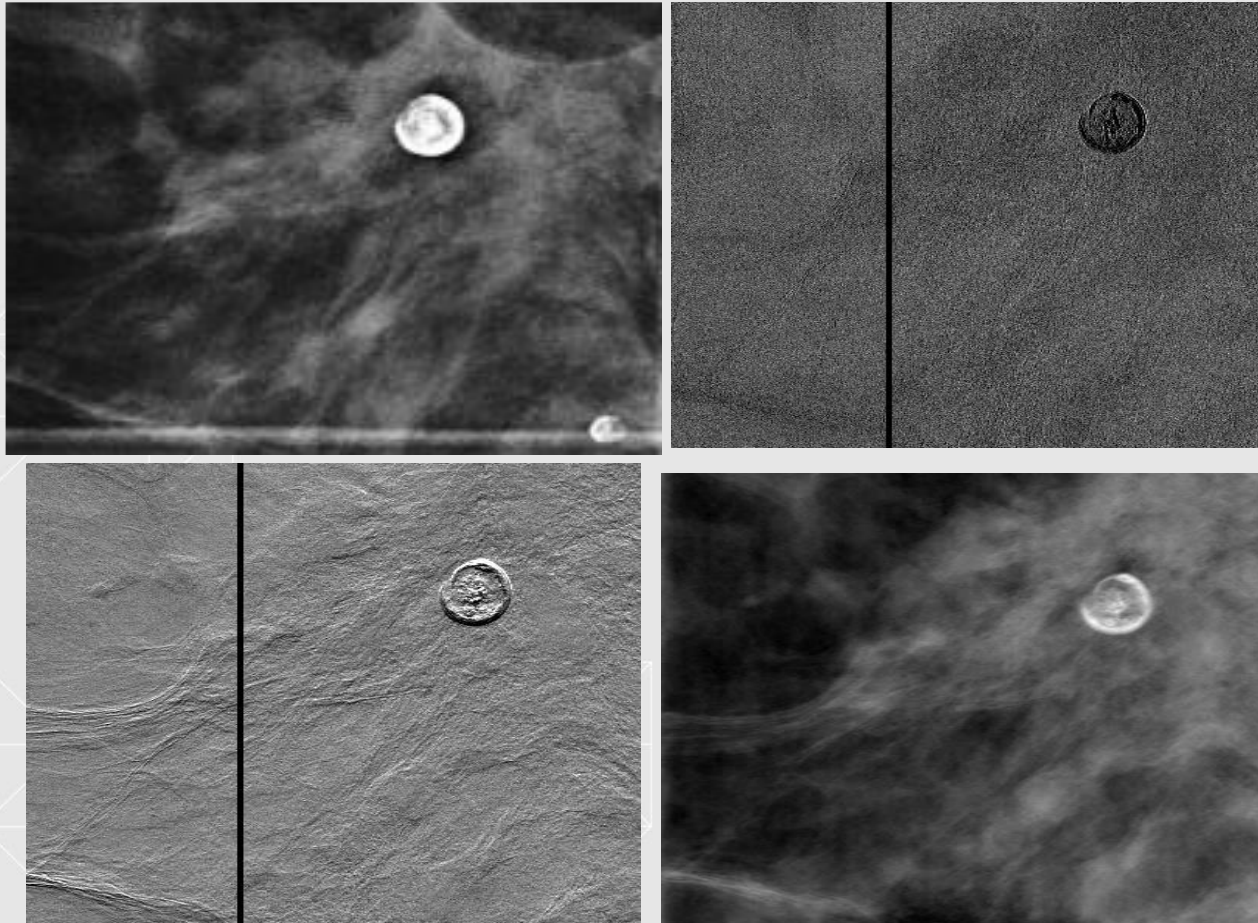
UCL



Use of ultra-high sensitivity to obtain significant dose reductions in mammography



UCL

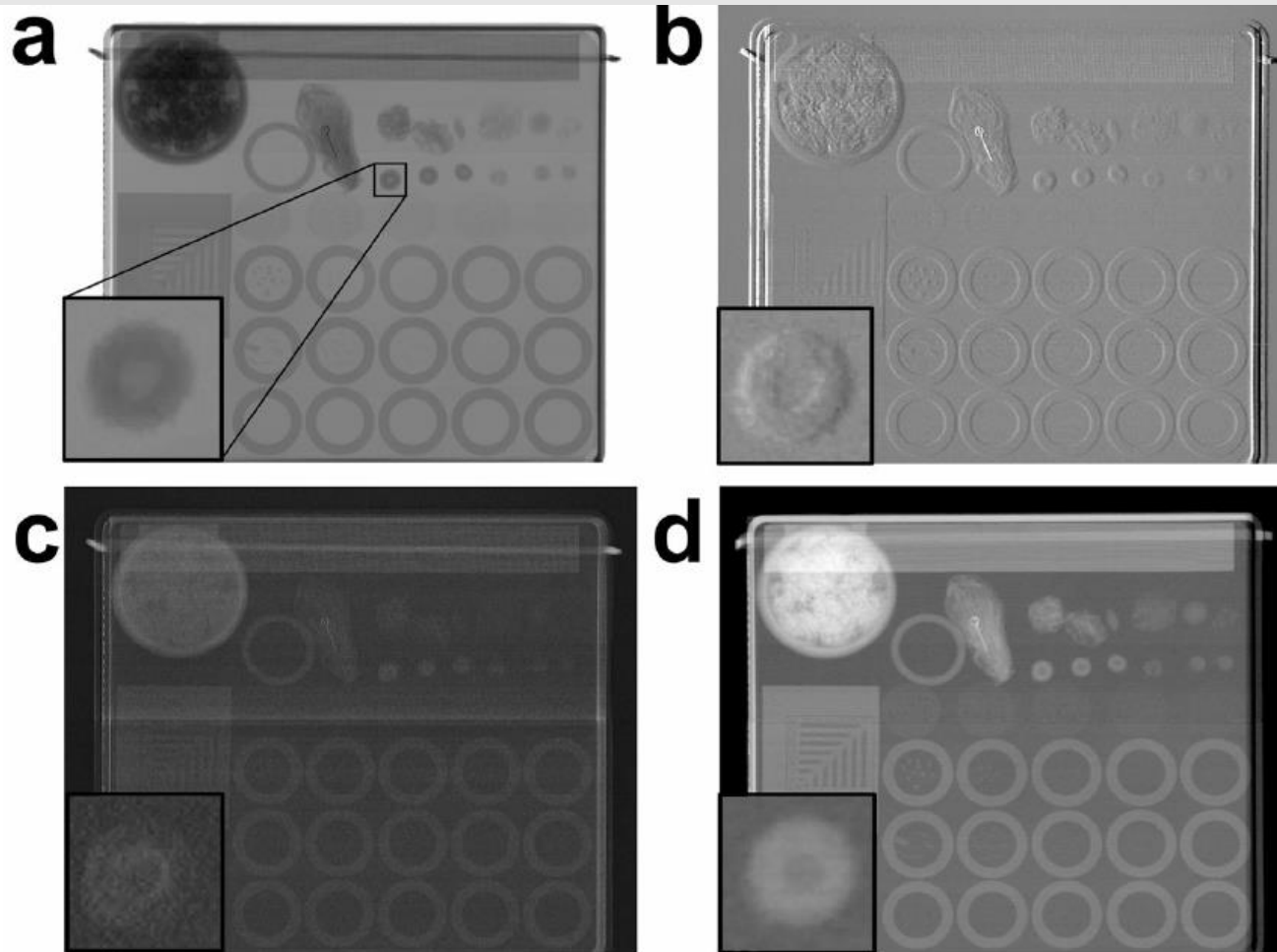


Total entrance dose = 0.115 mGy

First attempt at translation (on realistic, 5 cm thick mammo phantom)



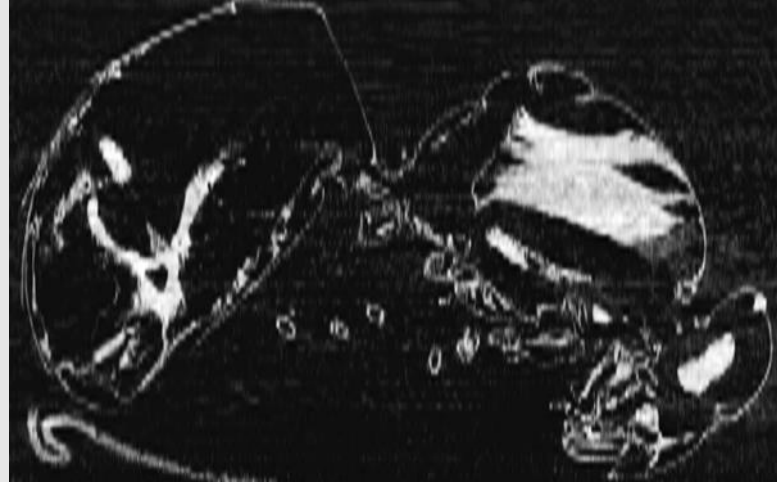
UCL



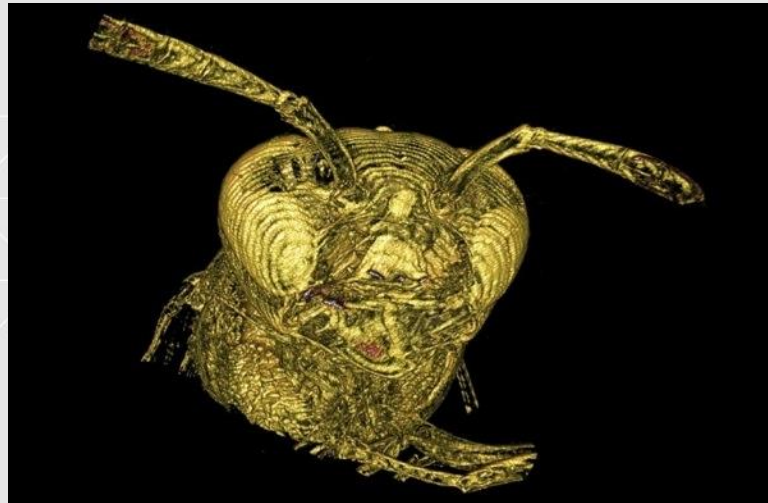
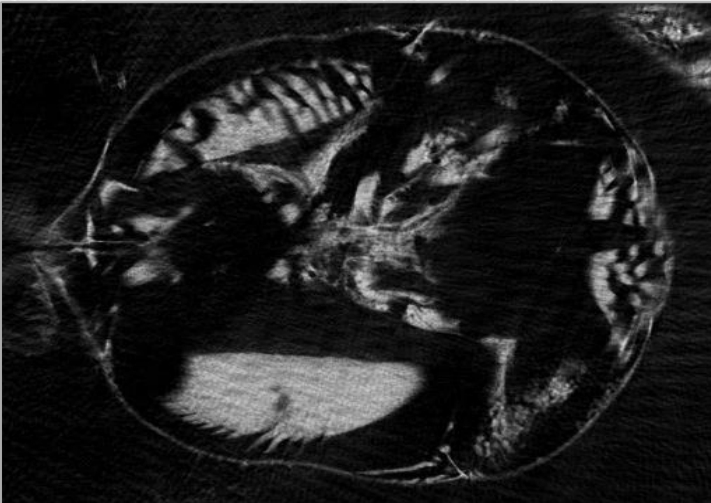
The pre-commercial system shown in the previous slide was used in two ways: a-c) multimodal use (attenuation, differential phase, dark field); **entrance** dose 2 mGy; d) “single-shot” retrieval, **entrance** dose 0.15 mGy.

To be compared with standard entrance doses in mammo of 10-12 mGy.

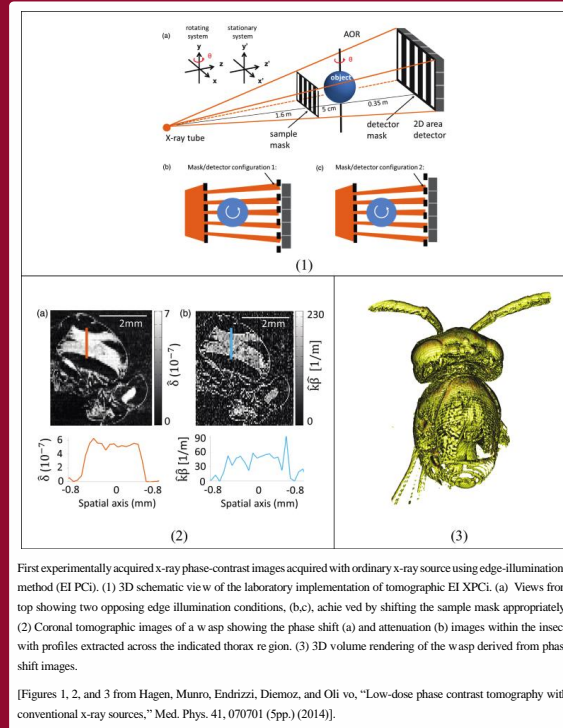
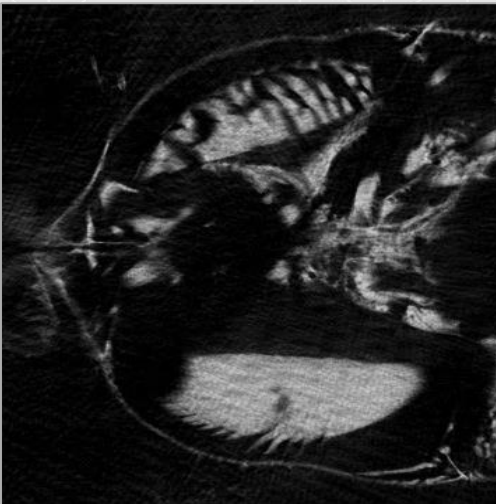
Early CT results



Soft tissue
inside wasp
thorax resolved



Dose **tens of
mGy**, instead
of tens of Gy!



First experimentally acquired x-ray phase-contrast images acquired with ordinary x-ray source using edge-illumination method (EI PCI). (1) 3D schematic view of the laboratory implementation of tomographic EI XPCI. (a) Views from top showing two opposing edge illumination conditions, (b,c), achieved by shifting the sample mask appropriately. (2) Coronal tomographic images of a wasp showing the phase shift (a) and attenuation (b) images within the insect with profiles extracted across the indicated thorax region. (3) 3D volume rendering of the wasp derived from phase shift images.

[Figures 1, 2, and 3 from Hagen, Munro, Endrizzi, Diemoz, and Oli vo, "Low-dose phase contrast tomography with conventional x-ray sources." *Med. Phys.* 41, 070701 (5pp.) (2014)].

Soft tissue
inside wasp
thorax resolved

Dose tens of
mGy, instead
of tens of Gy!

Published by the American Association of Physicists in Medicine (AAPM) with the association of the Canadian Organization of Medical Physicists (COMP), the Canadian College of Physicists in Medicine (CCPM), and the International Organization for Medical Physics (IOMP) through the AIP Publishing LLC. *Medical Physics* is an official science journal of the AAPM and of the COMP/CCPM/IOMP.

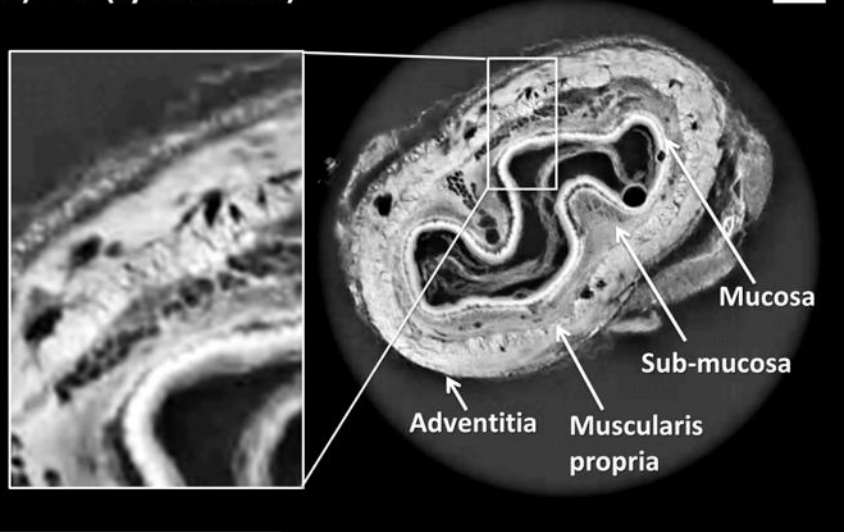
Medical Physics is a hybrid gold open-access journal.

First CT results

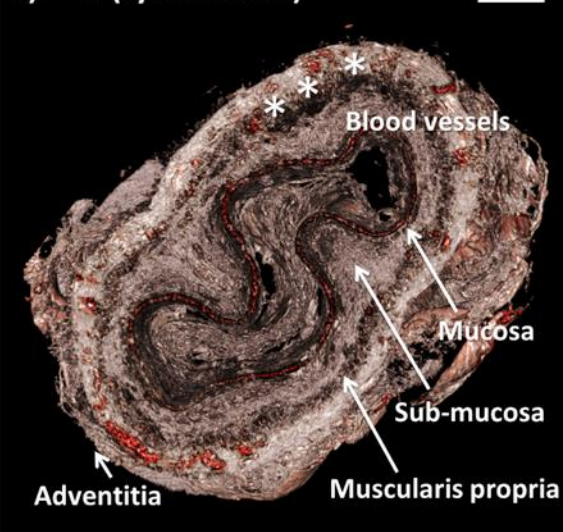
another example, fully decellularized tissue



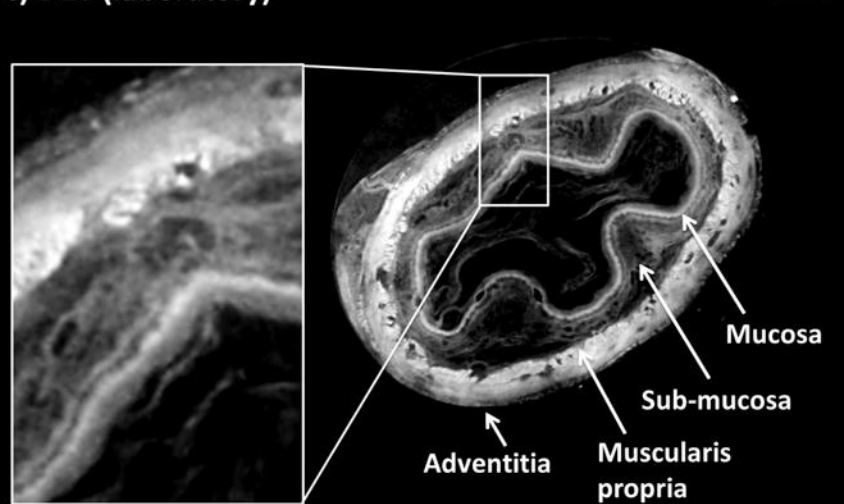
a) DET (synchrotron)



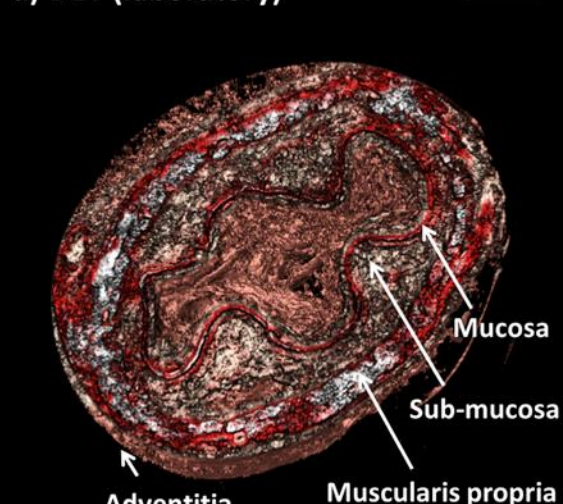
b) DET (synchrotron)



c) DET (laboratory)



d) DET (laboratory)



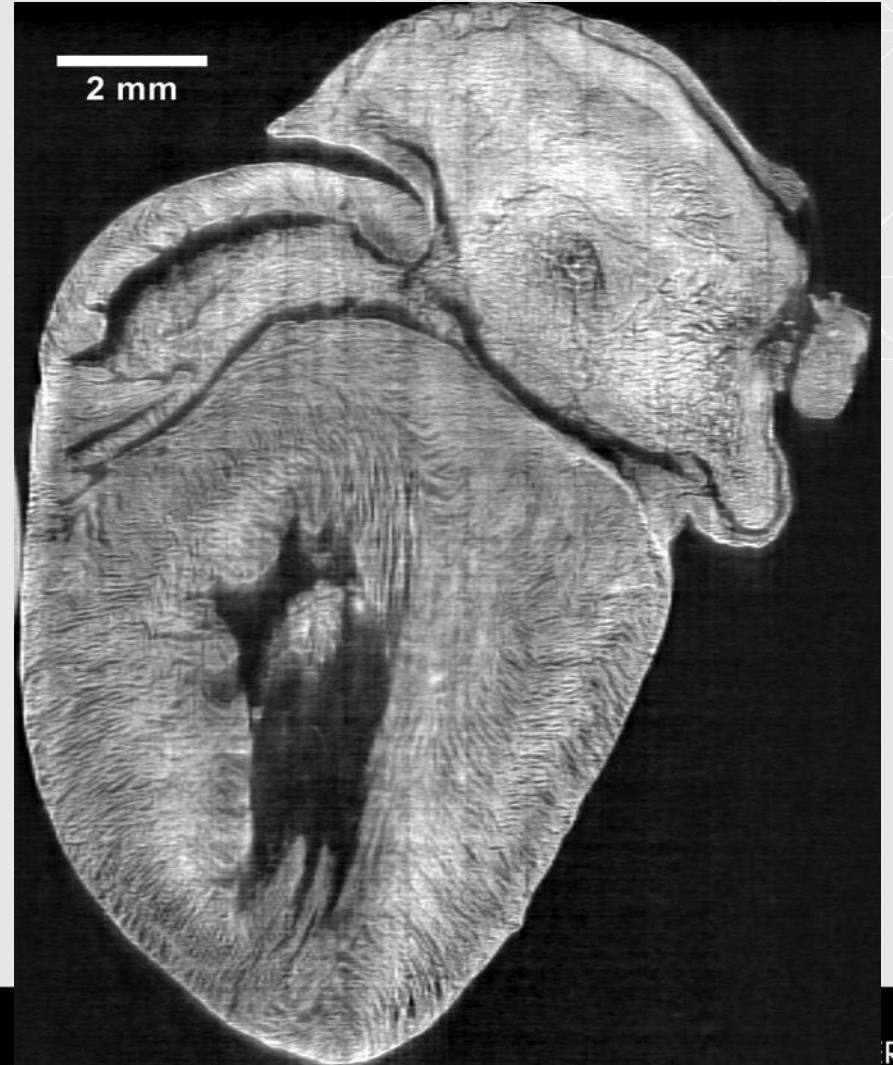
Rat heart



axial



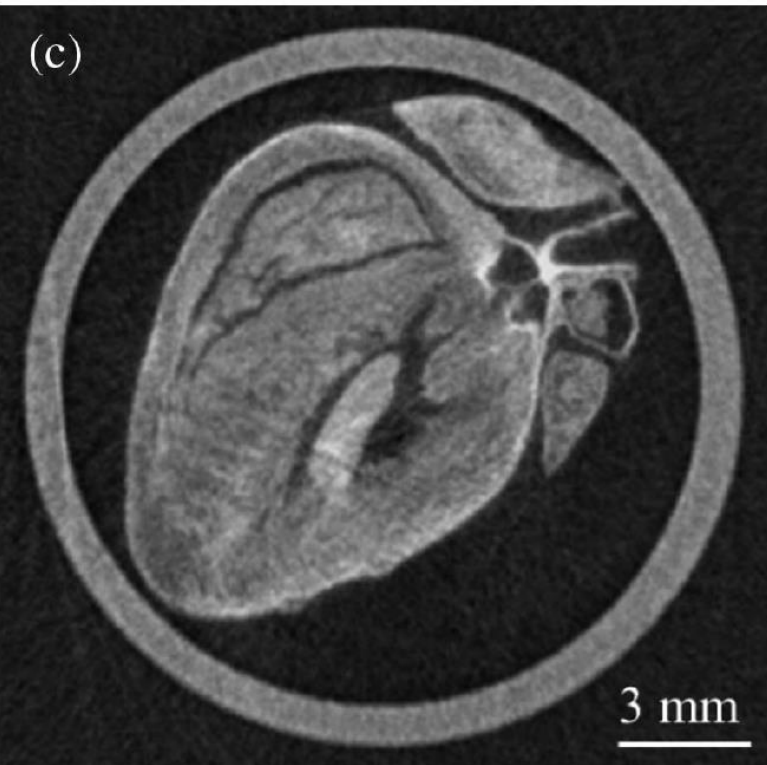
reslice



Rat heart – “single shot” lab CT version



This was obtained through *Diemoz's further adaptation of Paganin's single-shot retrieval* to the polychromatic case with laboratory sources.

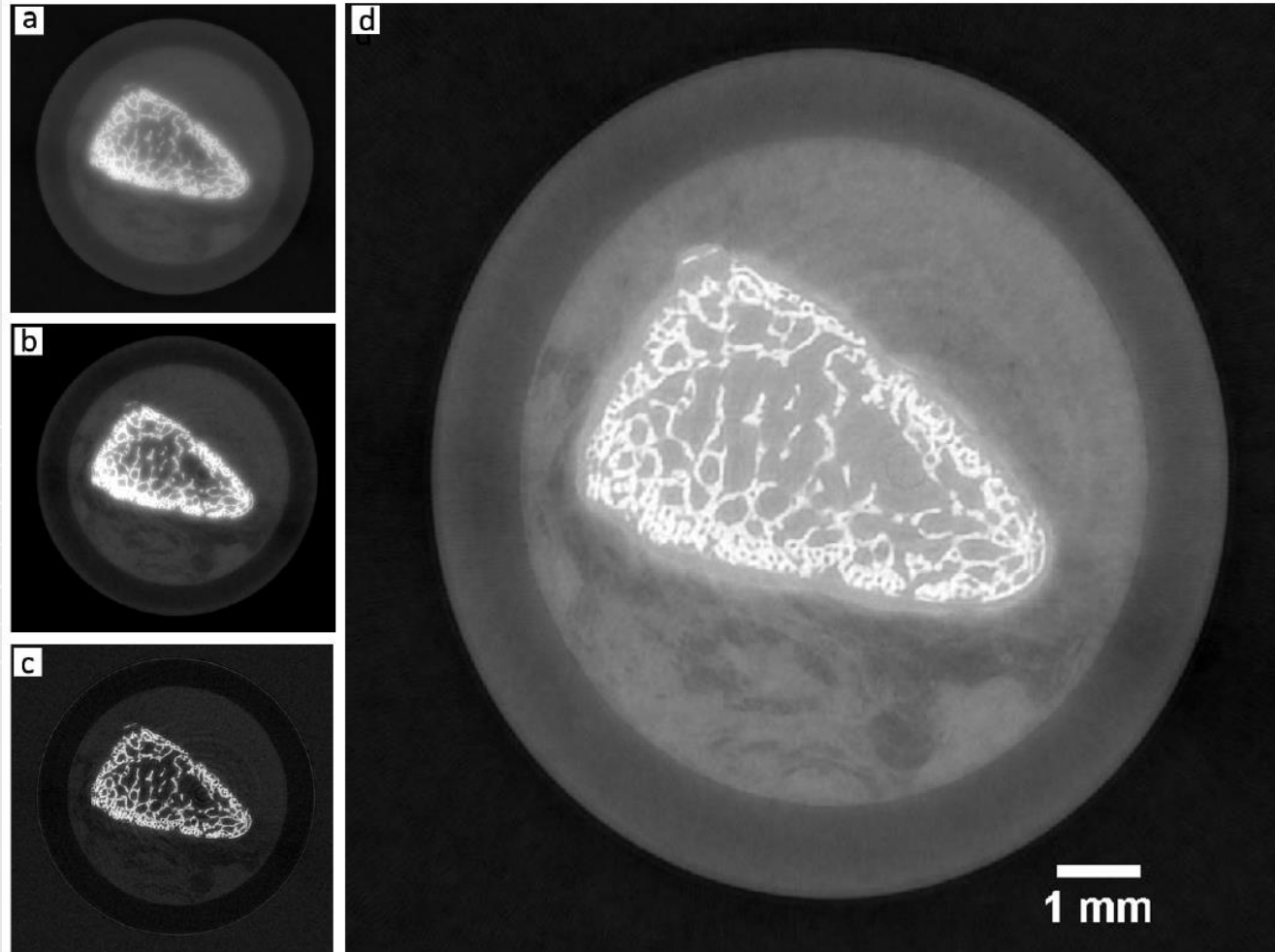


3' acquisition time. Previous record (EI + reverse projections, Hagen et al J. Phys. D: Appl. Phys. **49** (2016) 255501) was 25'. Most acquisitions reported in the literature take several hours.

Diemoz's method recently extended to non-homogeneous materials following the work of Beltran et al



UCL

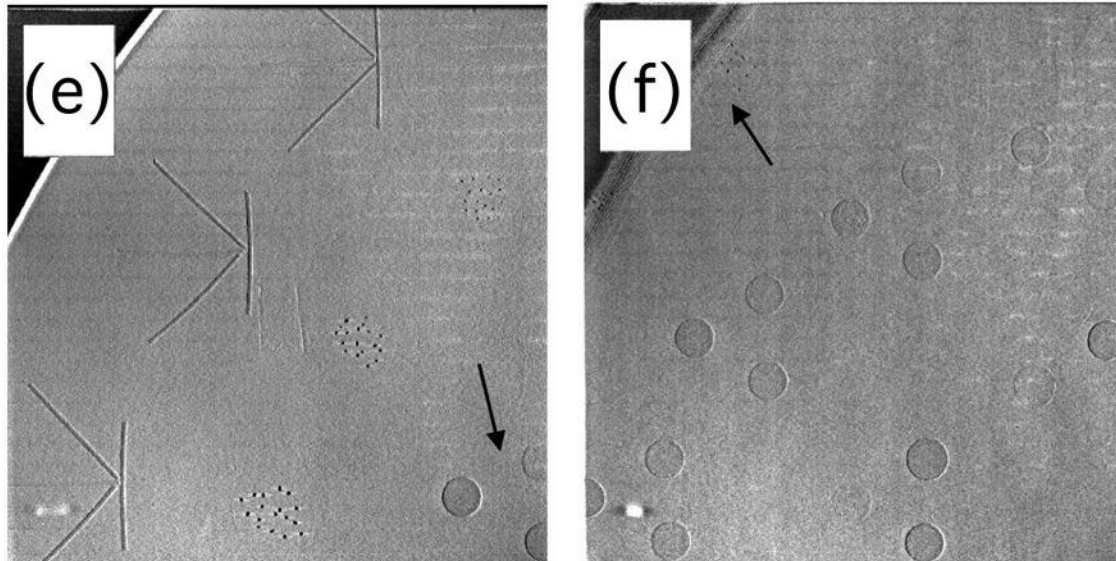
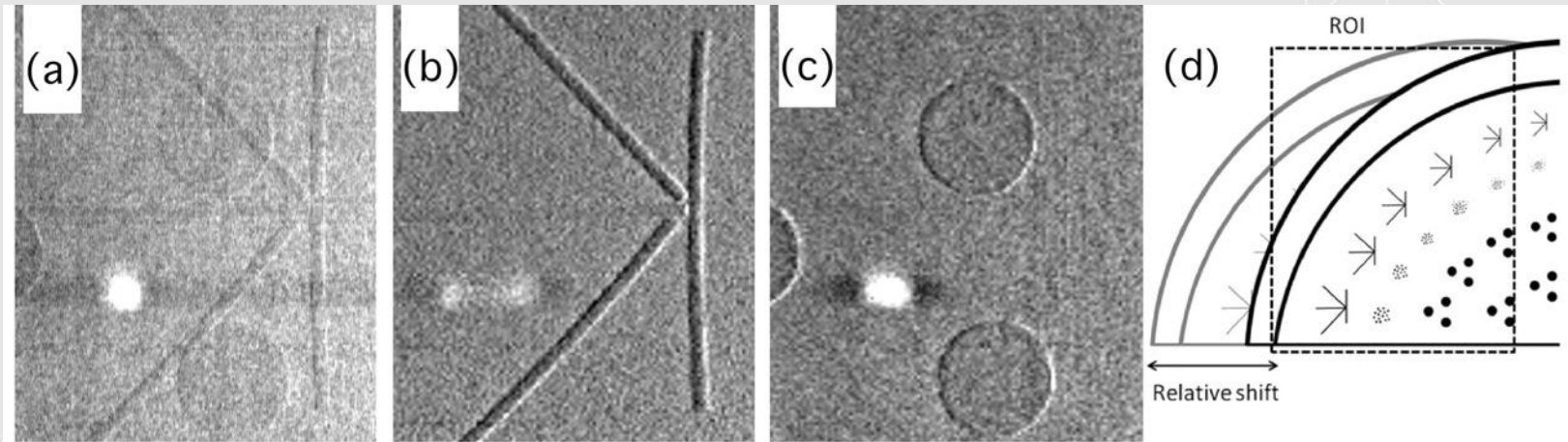


a) air-cylinder interface, b) intra-soft tissues, c) bone-soft tissue, d) spliced image. The paper also shows that the retrieved values are reliable through phantom work.

Phase-enhanced tomosynthesis:

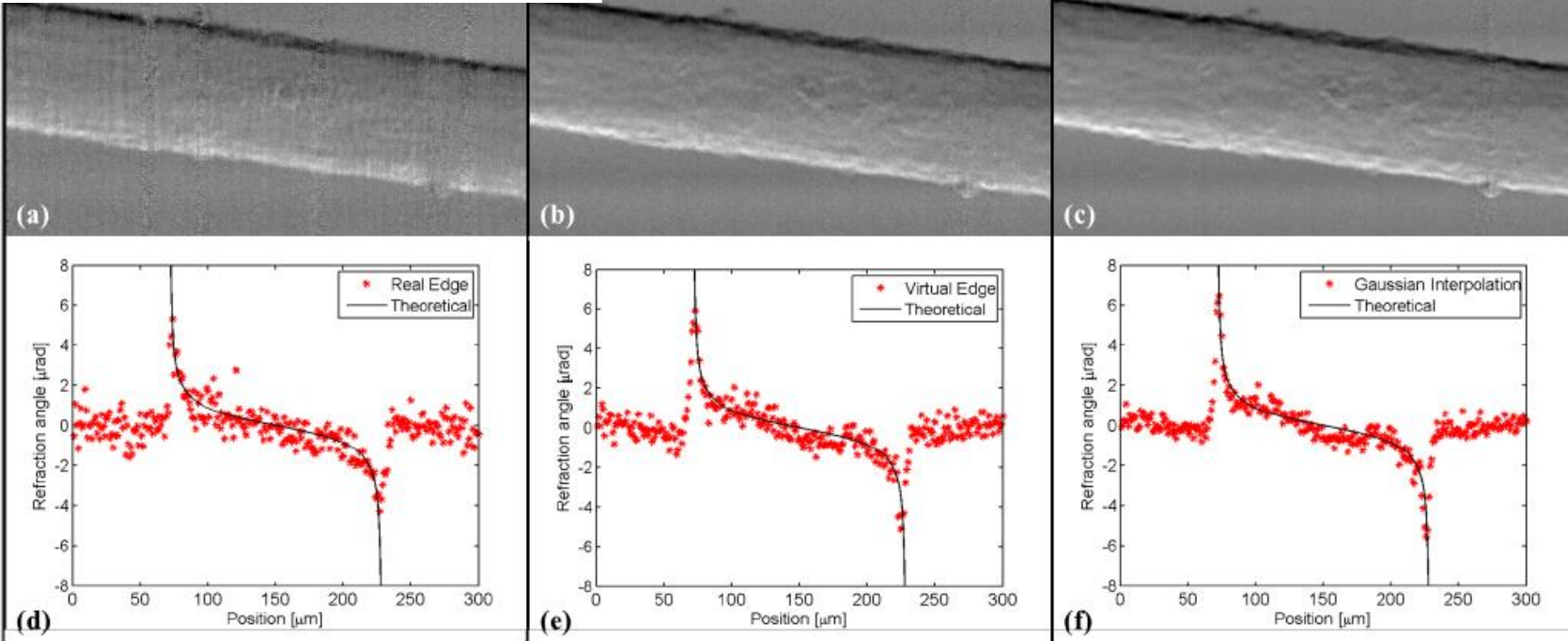
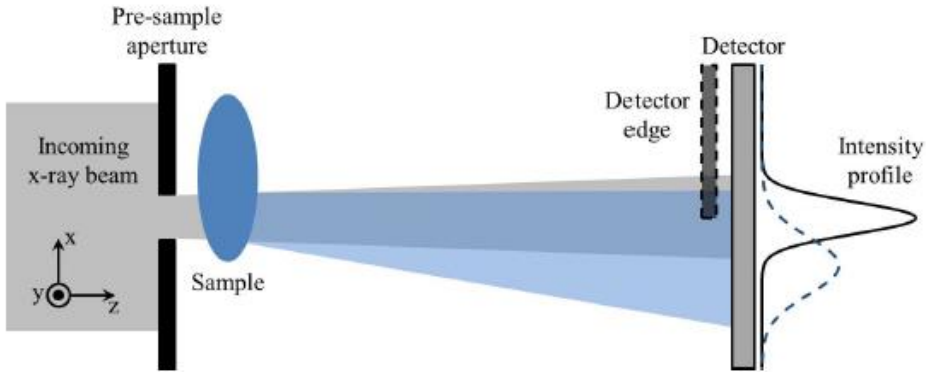


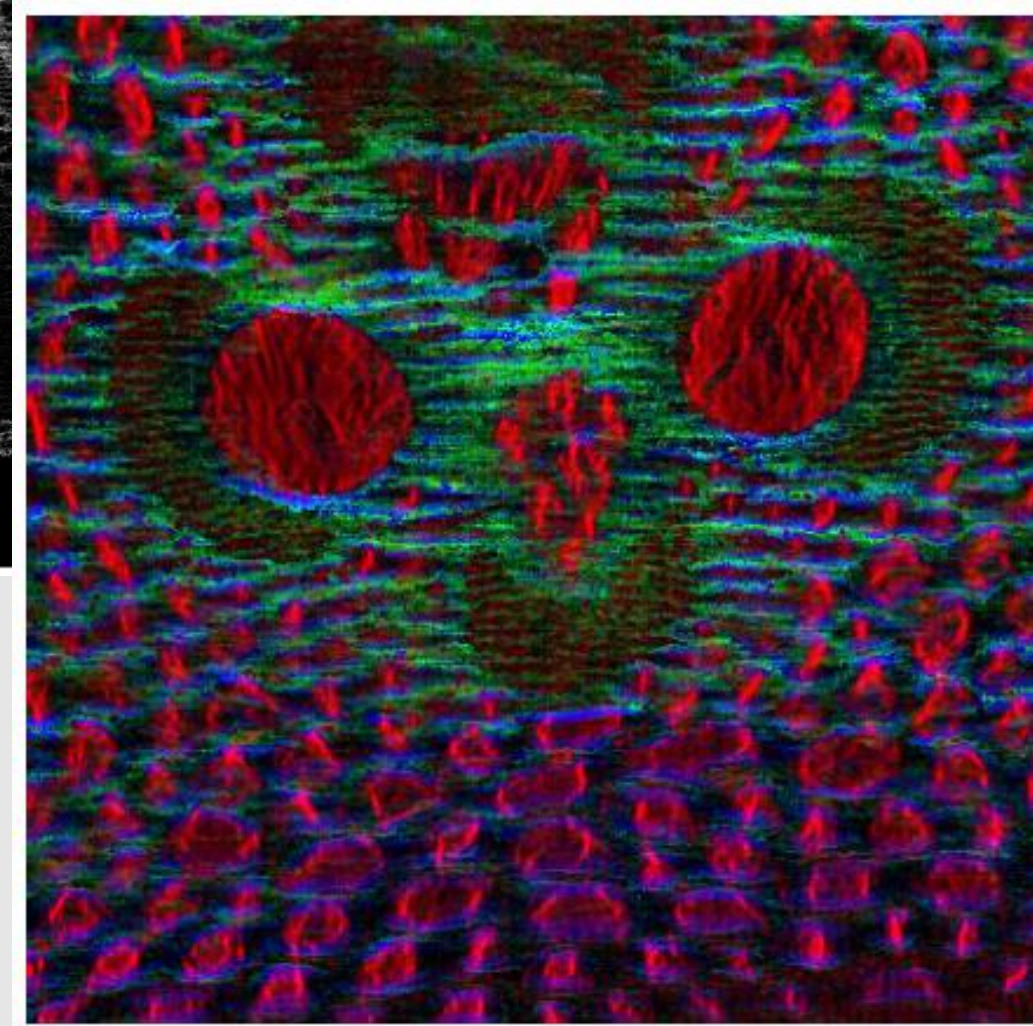
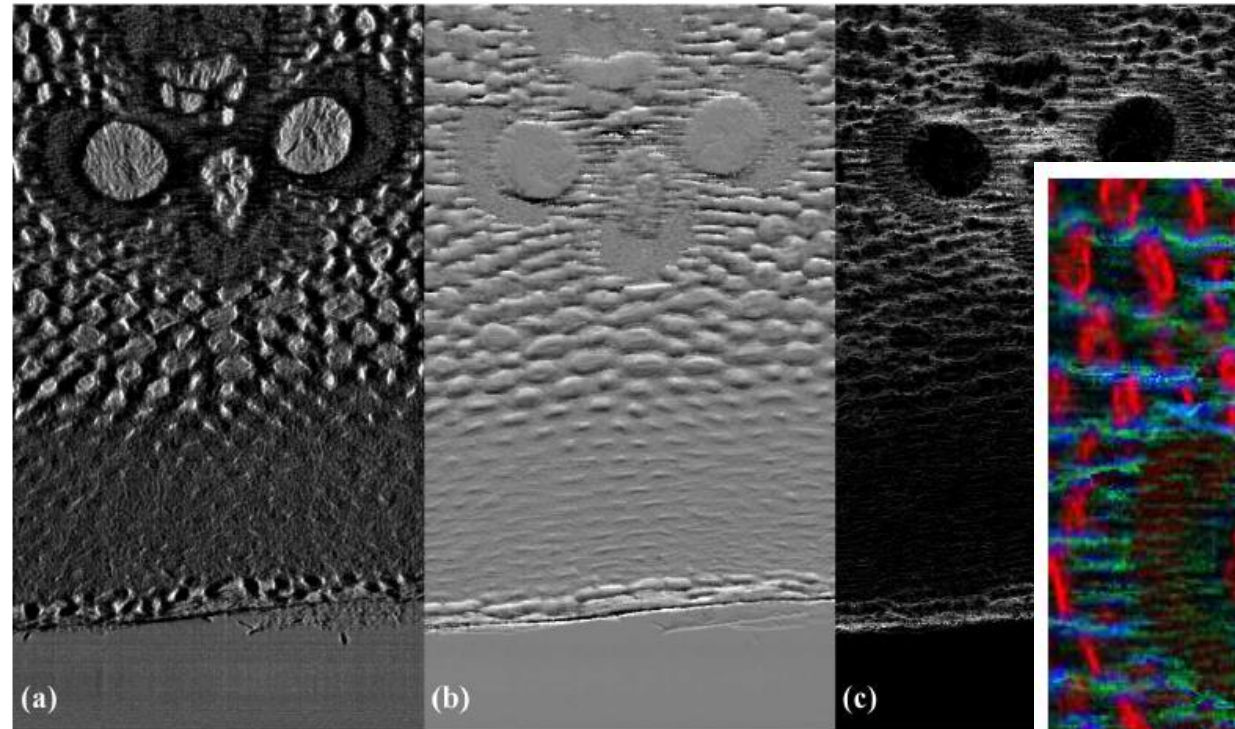
UCL



- 15 projections at 1° steps
- reconstructed with Dexela's proprietary "Separable Paraboloidal Surrogates" iterative algorithm
- Sample thickness 3.4 cm
- **TOTAL entrance dose 11 mGy** (compatible with mammo)

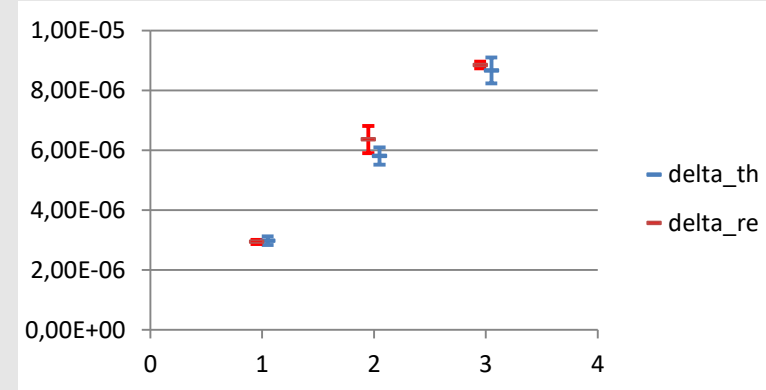
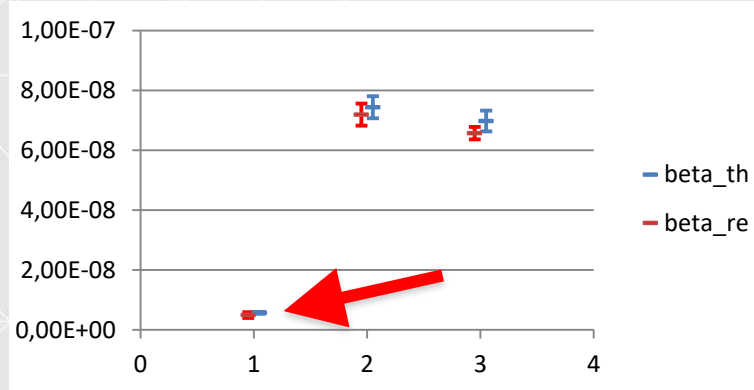
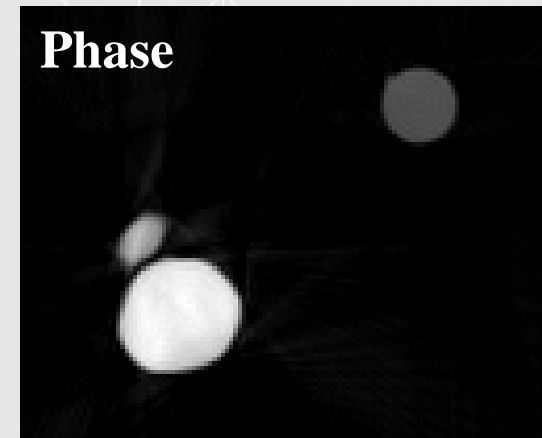
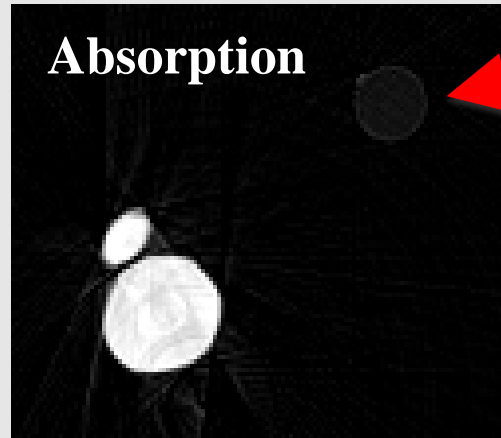
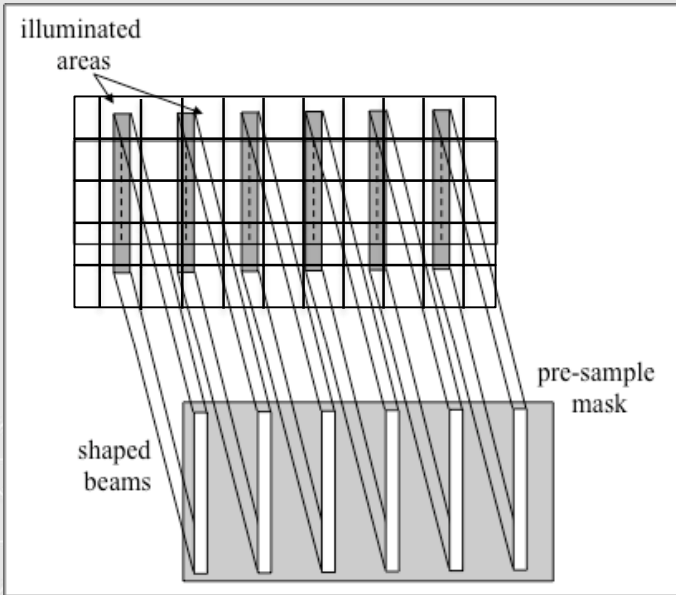
“virtual” edge/beam tracking



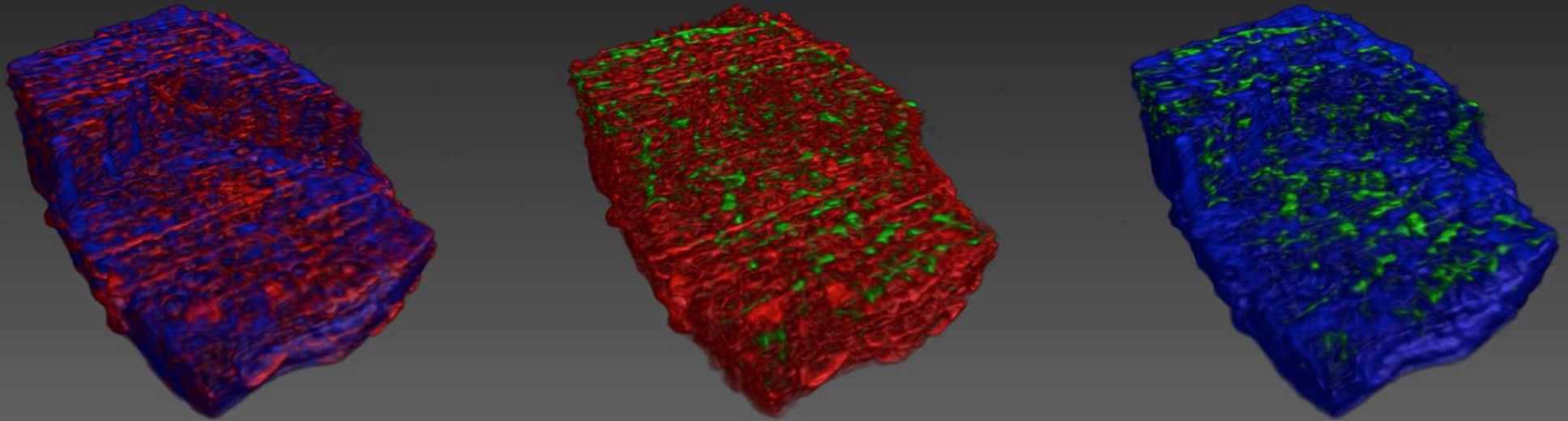


R abs
B |refr|
G scatt

beam tracking – can be extended to CT via a mask



beam tracking – can be extended to CT via a mask



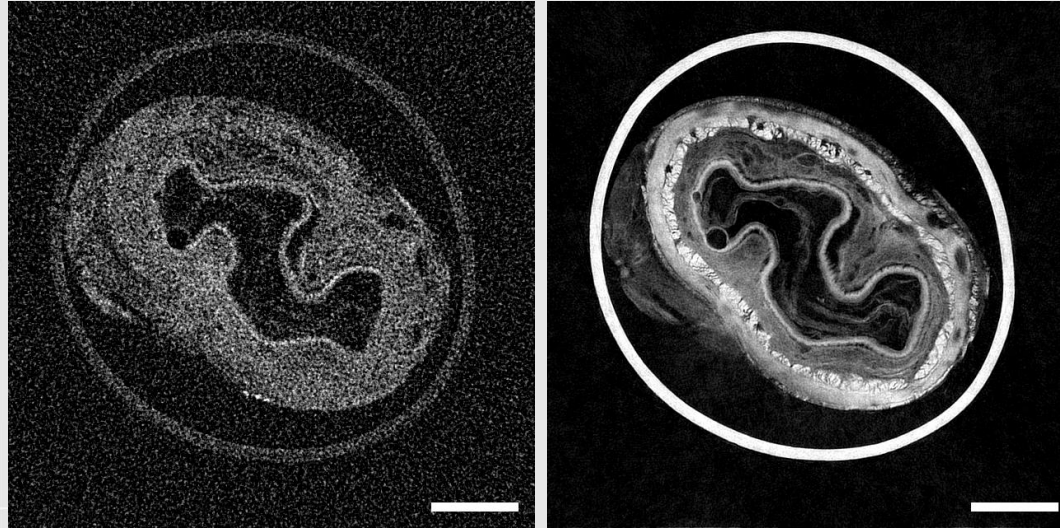
attenuation **phase** **scattering**

translated to the lab, seems to work even better than the synchrotron! (trying to understand why before we publish...)

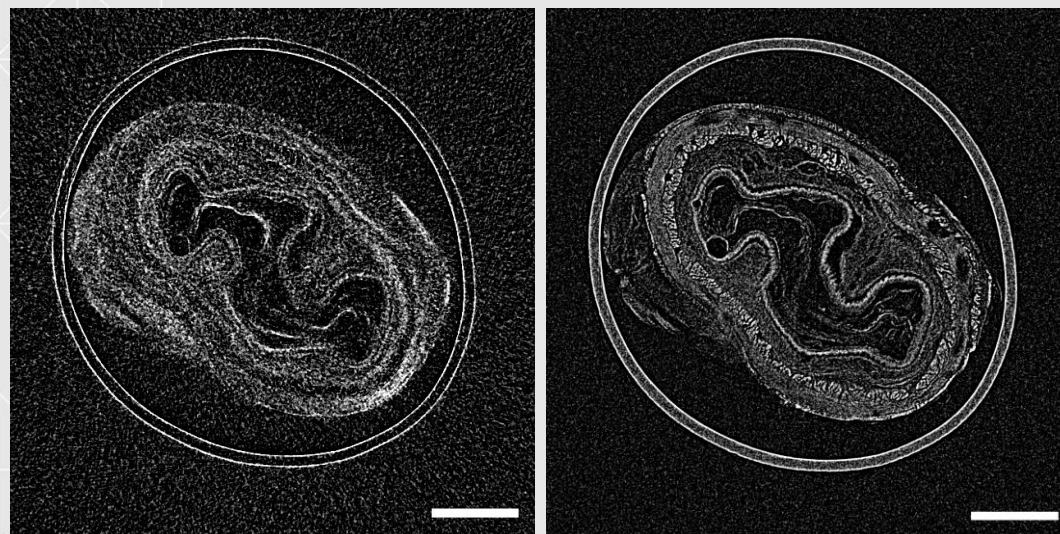


This is best of both worlds – as many photons as in the attenuation image, plus the enhanced contrast coming from the phase...

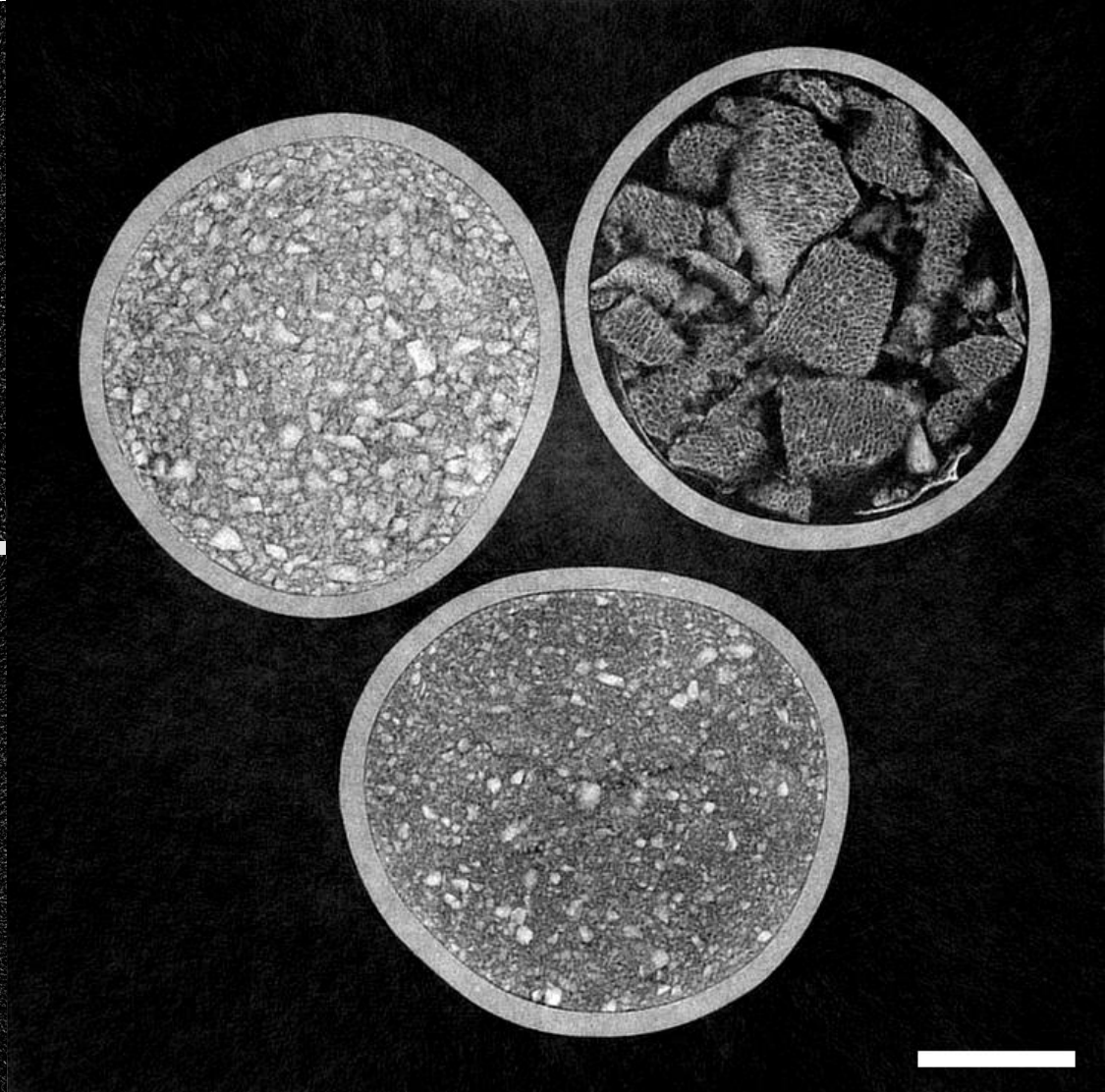
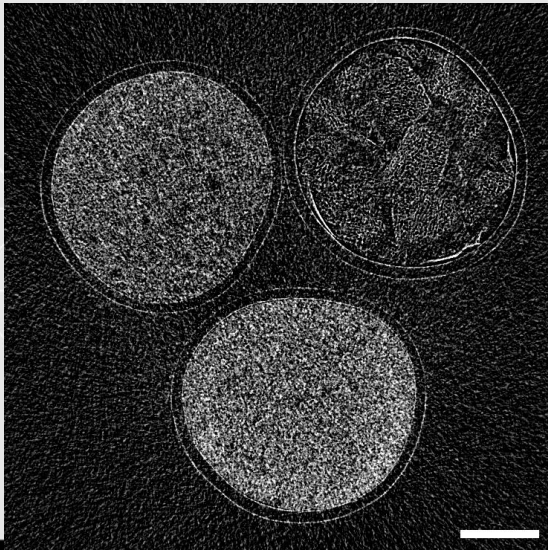
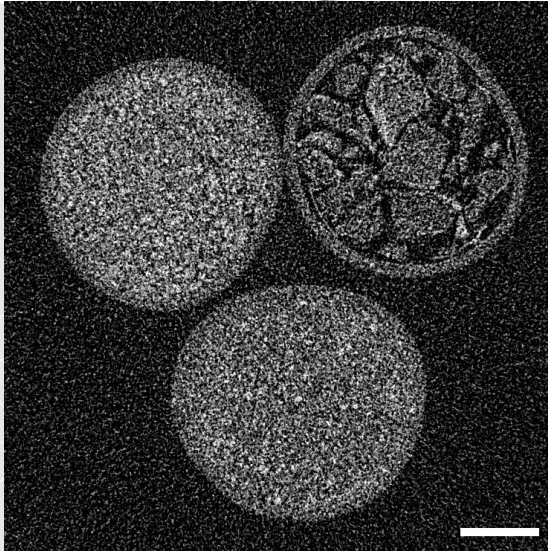
NB: here visibility is low because there just isn't enough contrast..



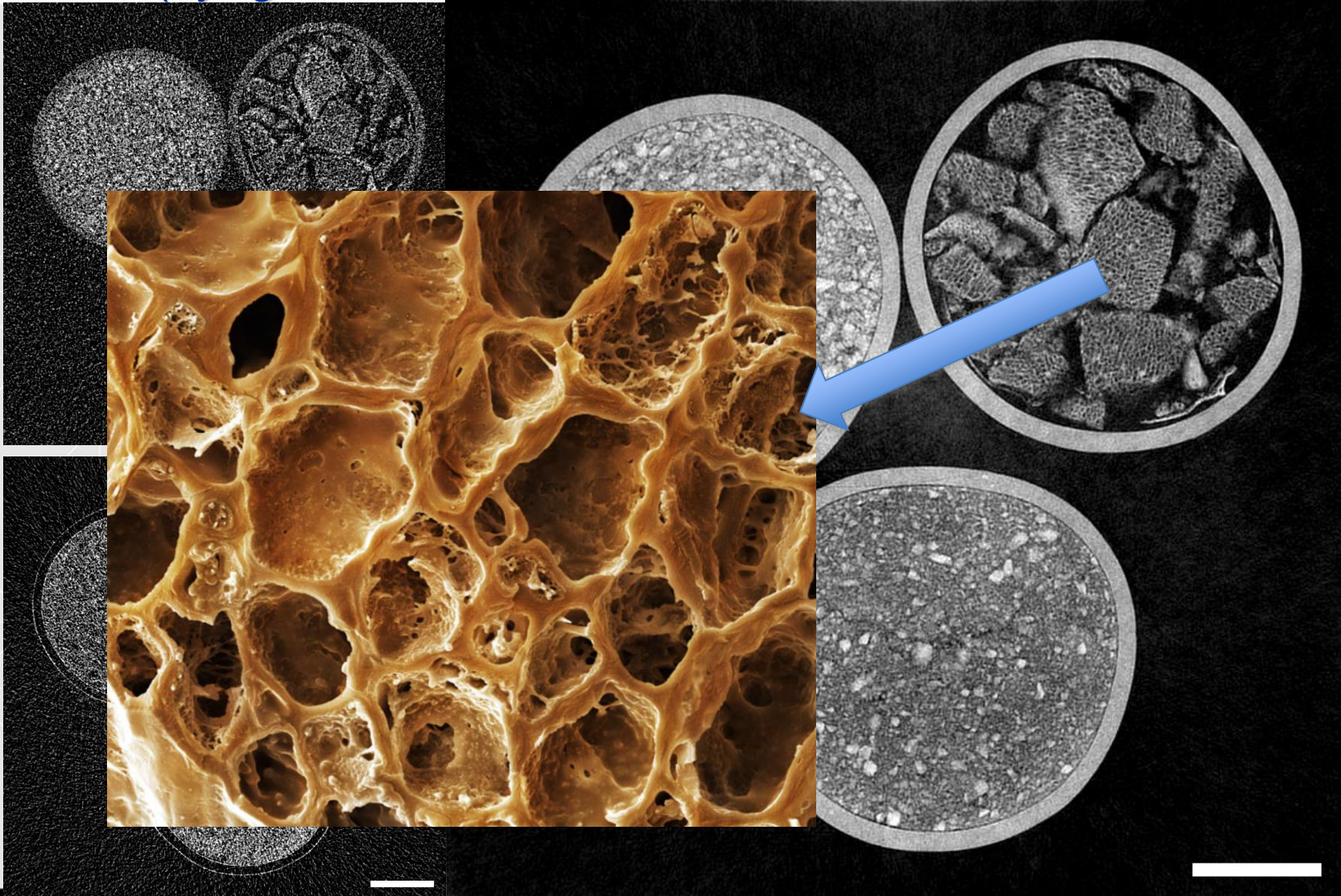
While here it is low because contrast is high, the number of scattered photons is low! (however it shows complementary features)



translated to the lab, seems to work even better than the synchrotron! (trying to understand why before we publish...)



translated to the lab, seems to work even better than the synchrotron! (trying to understand why before we publish...)



Conclusions



UCL

XPCI has transformative potential on a range of applications – medical and not.

For years it has been considered restricted to synchrotrons, but techniques have emerged that enable implementations with conventional sources – opening the way to translation opportunities.

Several hurdles must be overcome - including system stability, scalability, alignment etc. The key ones are arguably **excessive dose and acquisition time**.

Our group is focusing on edge-illumination XPCi because we find that its **non-interferometric, virtually incoherent** nature (while remaining **quantitative**) makes it suitable for translation into real-world systems.

One key aspect is the possibility to implement **single-shot methods**, avoiding having to displace optical elements between acquisitions etc. We see this as absolutely essential in CT – e.g. continuous sample rotation is otherwise impossible.

By exploiting these properties, we managed to reach **delivered doses and acquisition times compatible with real-world uses**.



BIG THANKS TO:



<https://www.ucl.ac.uk/medphys/research/axim>

