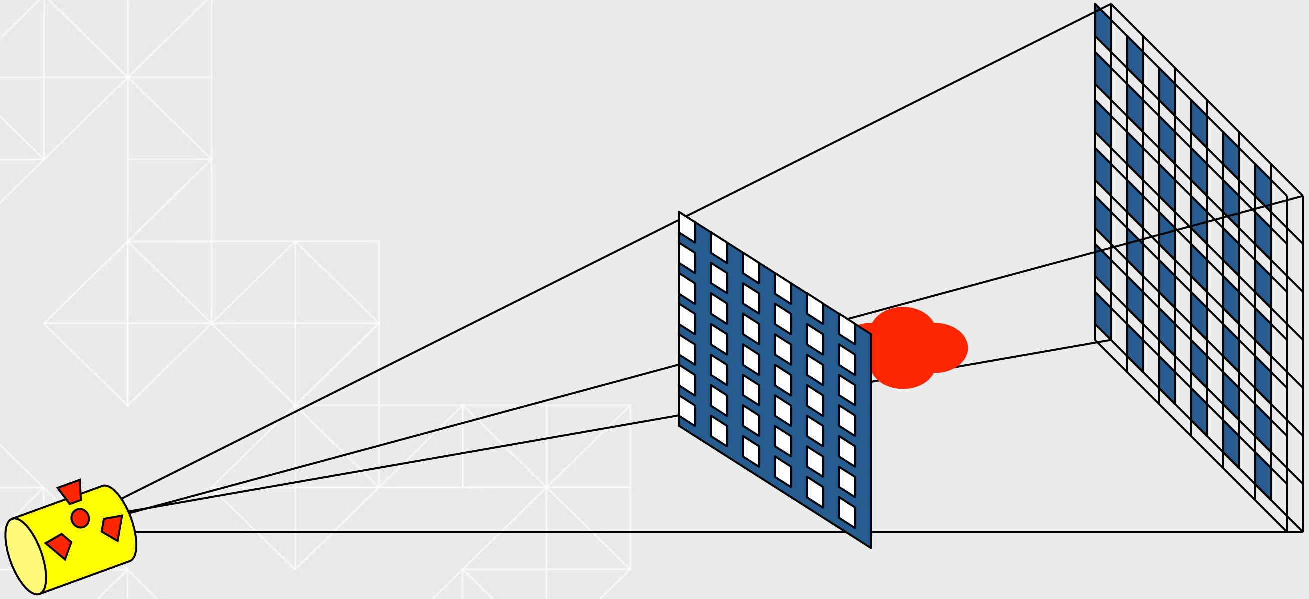
UCL ENGINEERING

Prospective use of laser-driven sources for x-ray phase contrast imaging

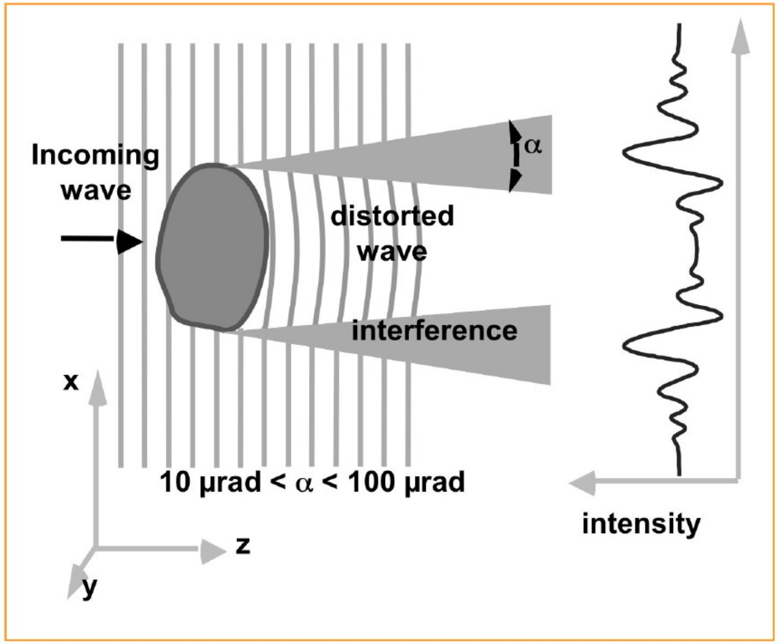


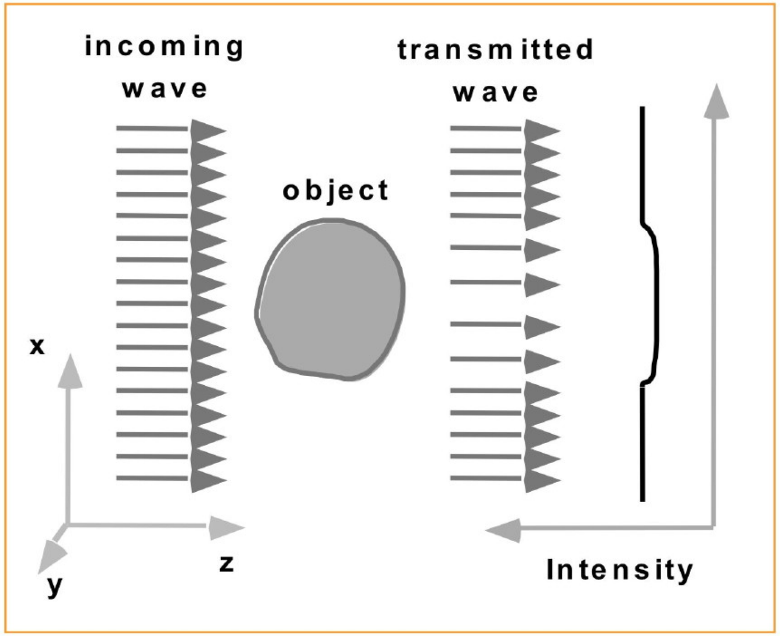
Sandro Olivo, Head, UCL XPCi/AXIm group
Medical Physics and Bioemedical Engineering, UCL

EuroNNAC and EuPRAXIA Workshop on Pilot Applications of Electron Plasma Accelerators (PAEPA), Ecole Polytechnique, Palaiseau, France, Oct 11-13, 2016

UCL ENGINEERING
Change the world

Phase Contrast Imaging vs. Conventional Radiology



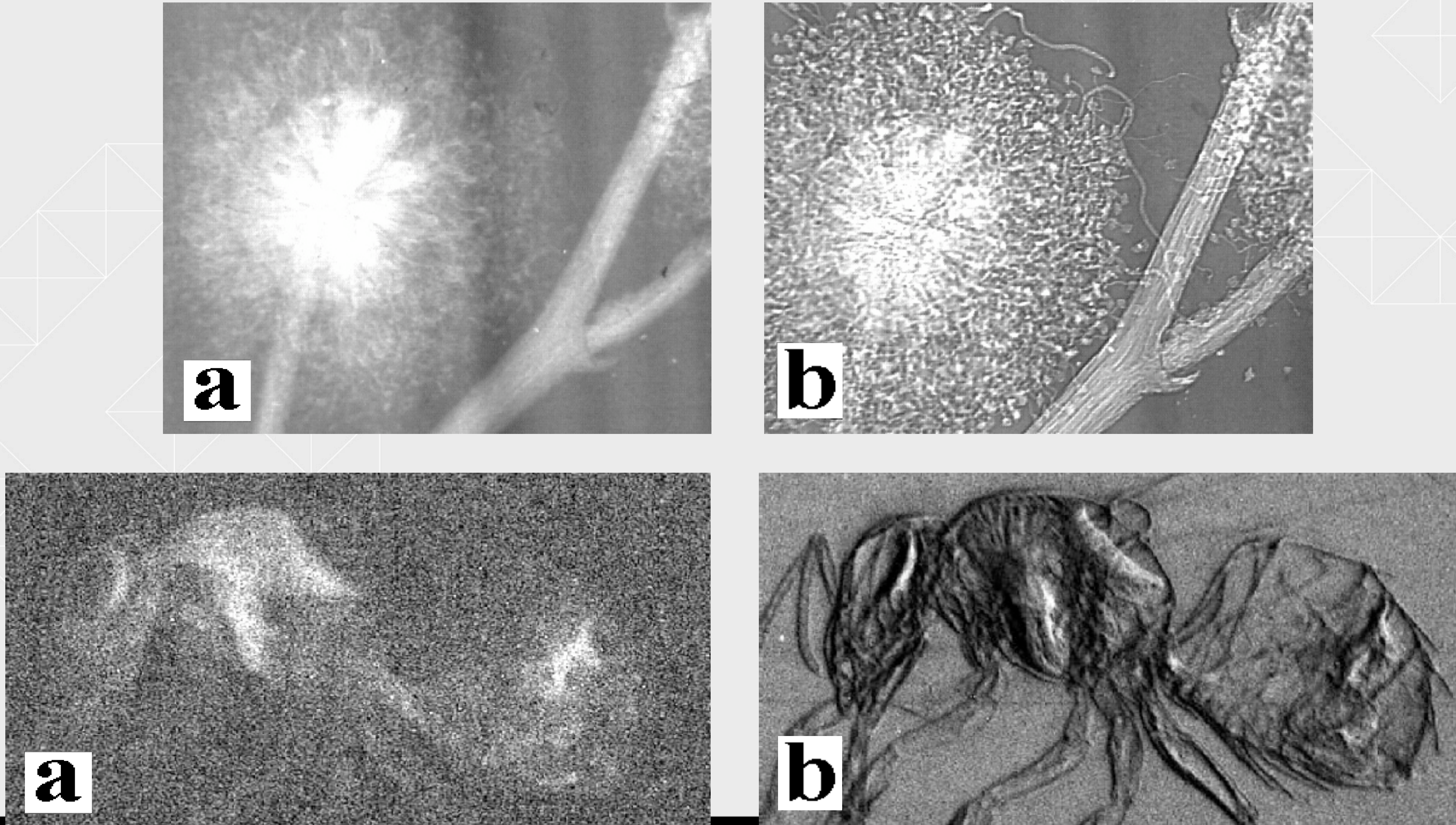


Refractive index: $n = 1 - \delta + i\beta$; $\delta >> \beta$ ->

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

Two possible approaches:
- **detect interference patterns**
- **detect angular deviations**

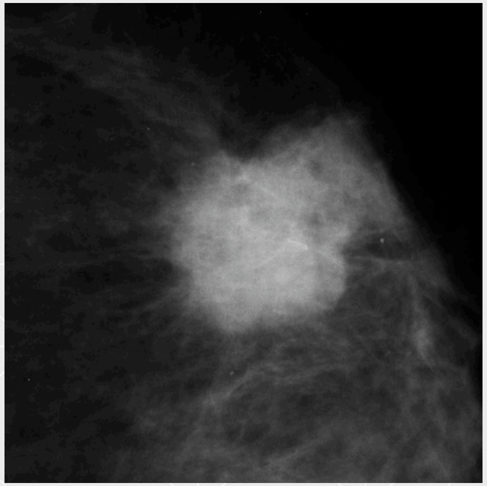
a) absorption b) phase contrast



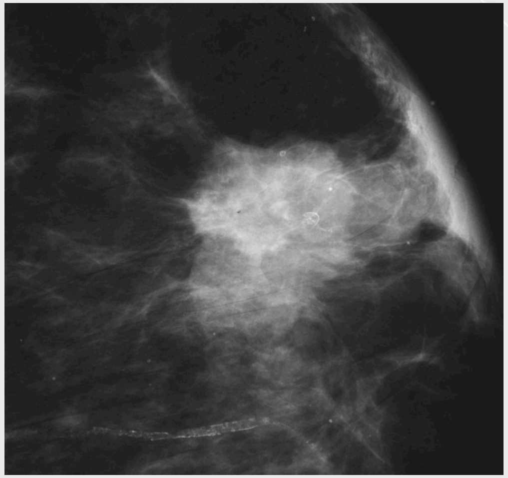
DiMichiel *et al* Proceedings of MASR1997

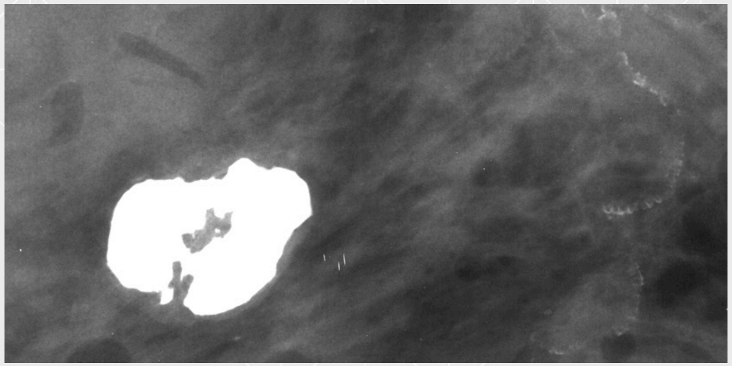
Impressive results are achieved in breast imaging

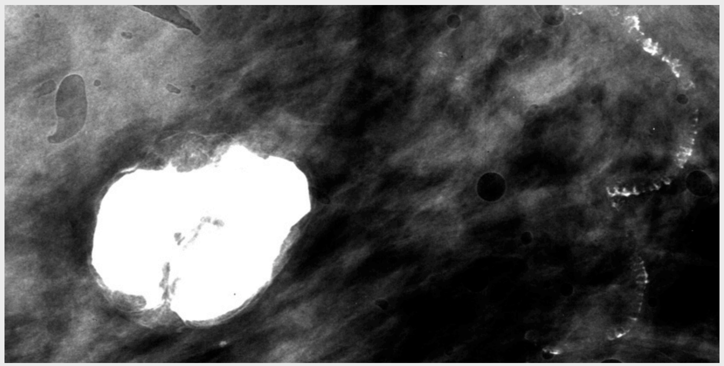
absorption



phase contrast

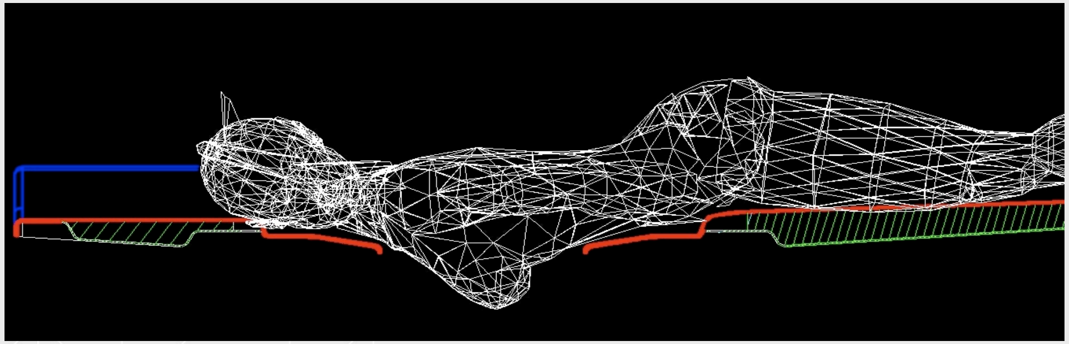


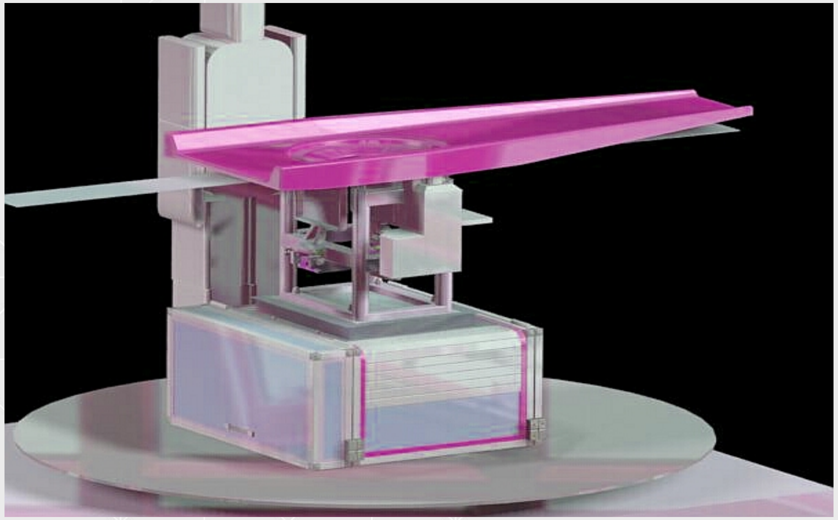


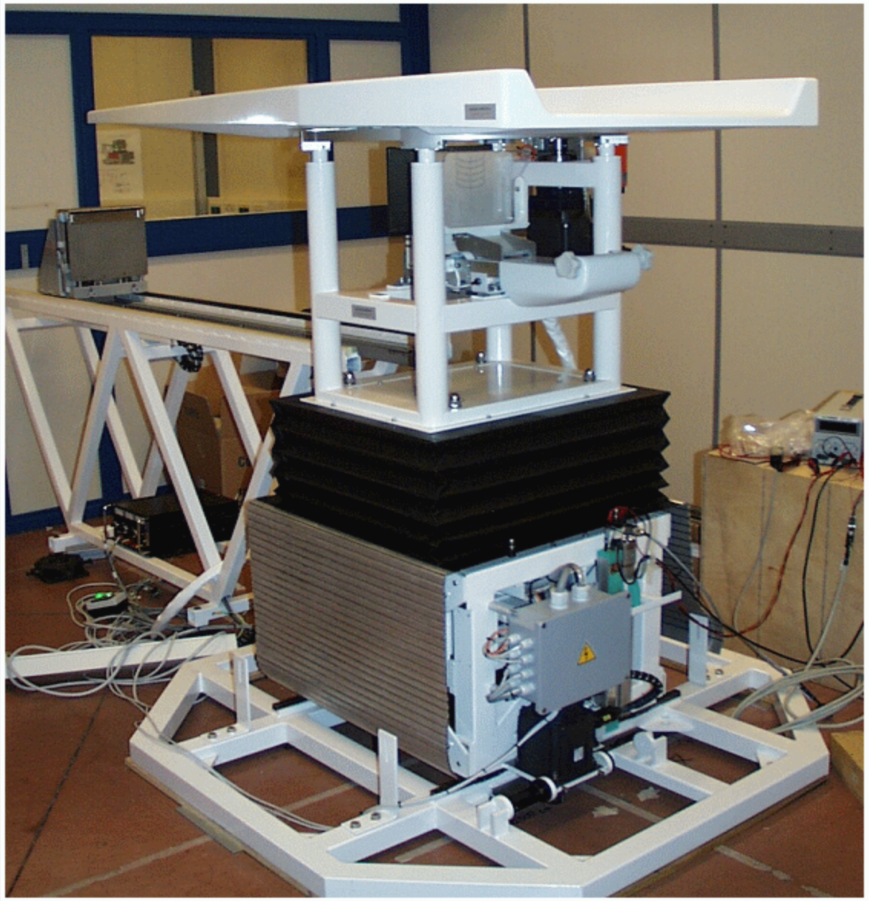


Arfelli et al. Phys. Med. Biol. 43 (1998) 2845-52

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

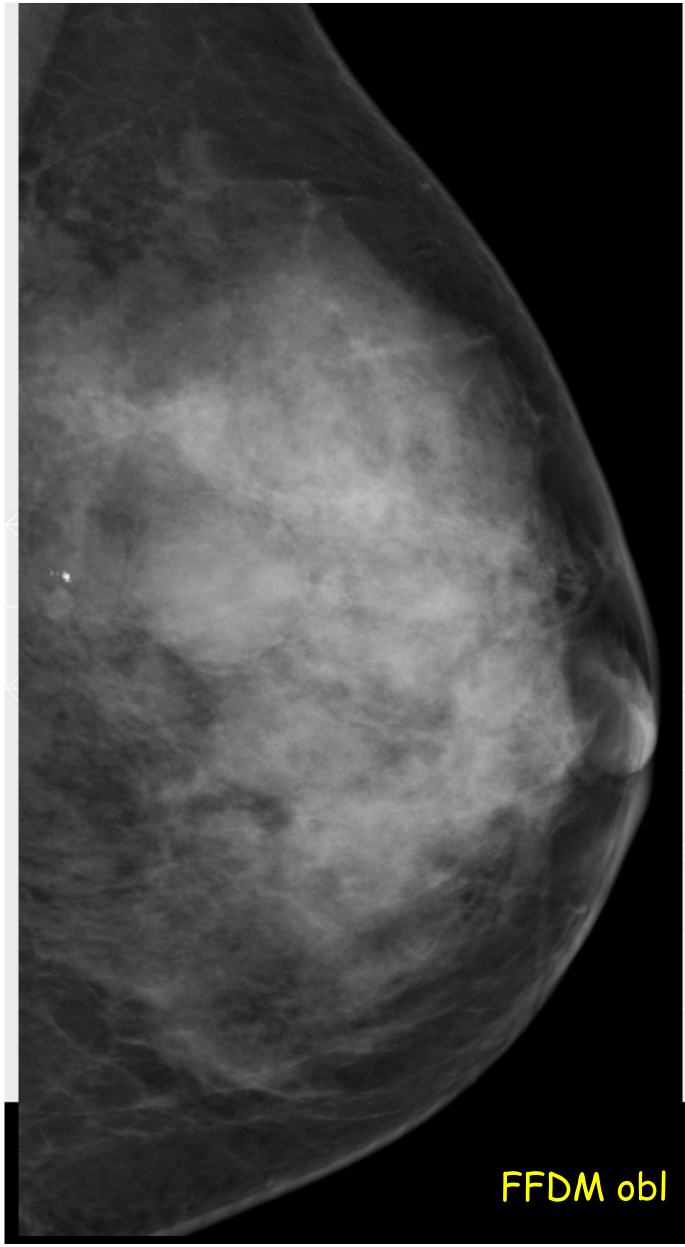


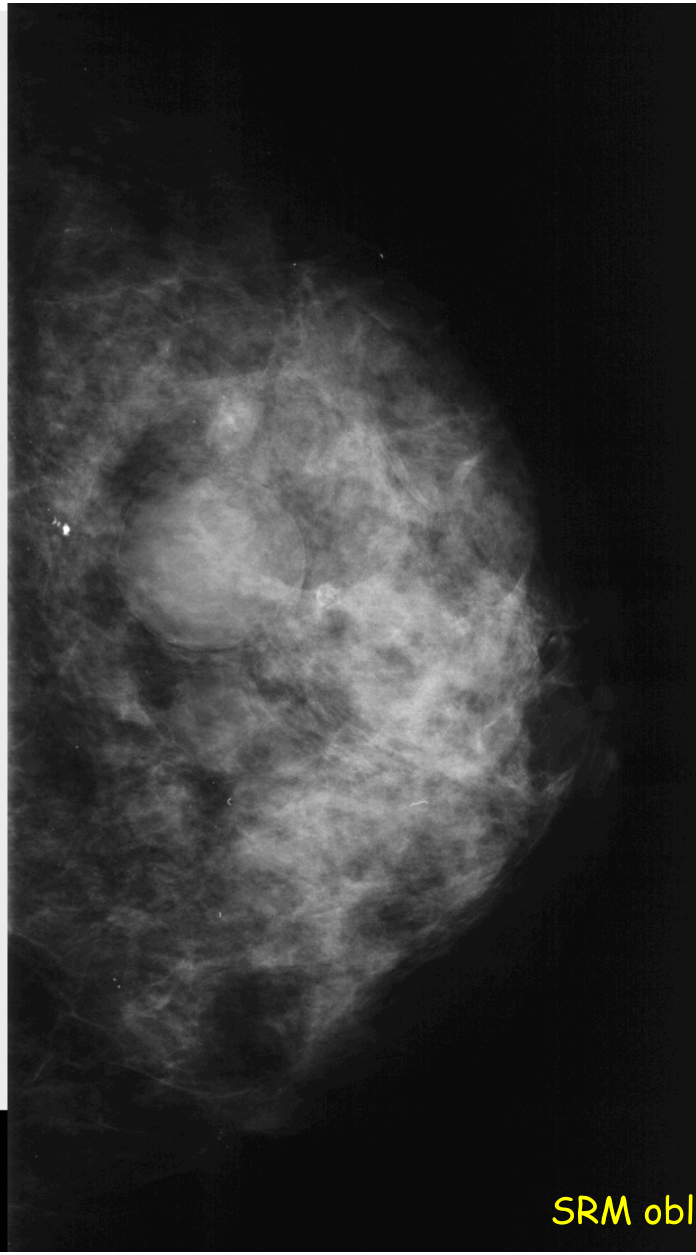




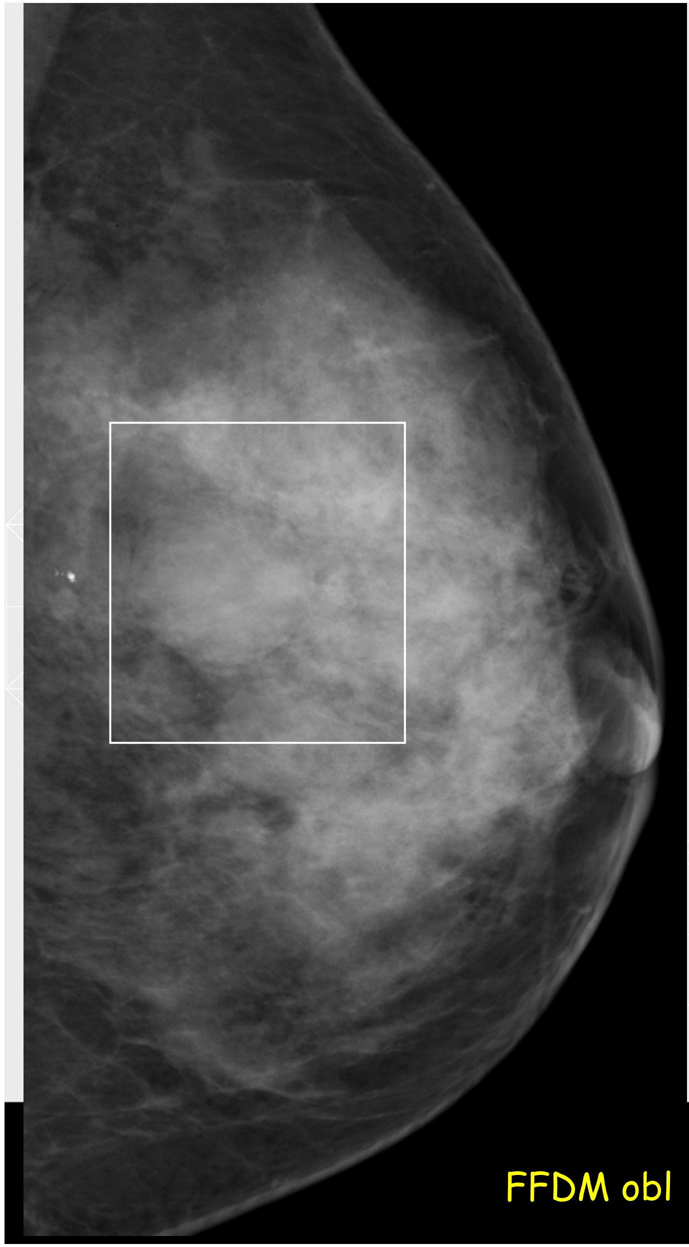
Castelli et al. Radiology 259 (2011) 684-94

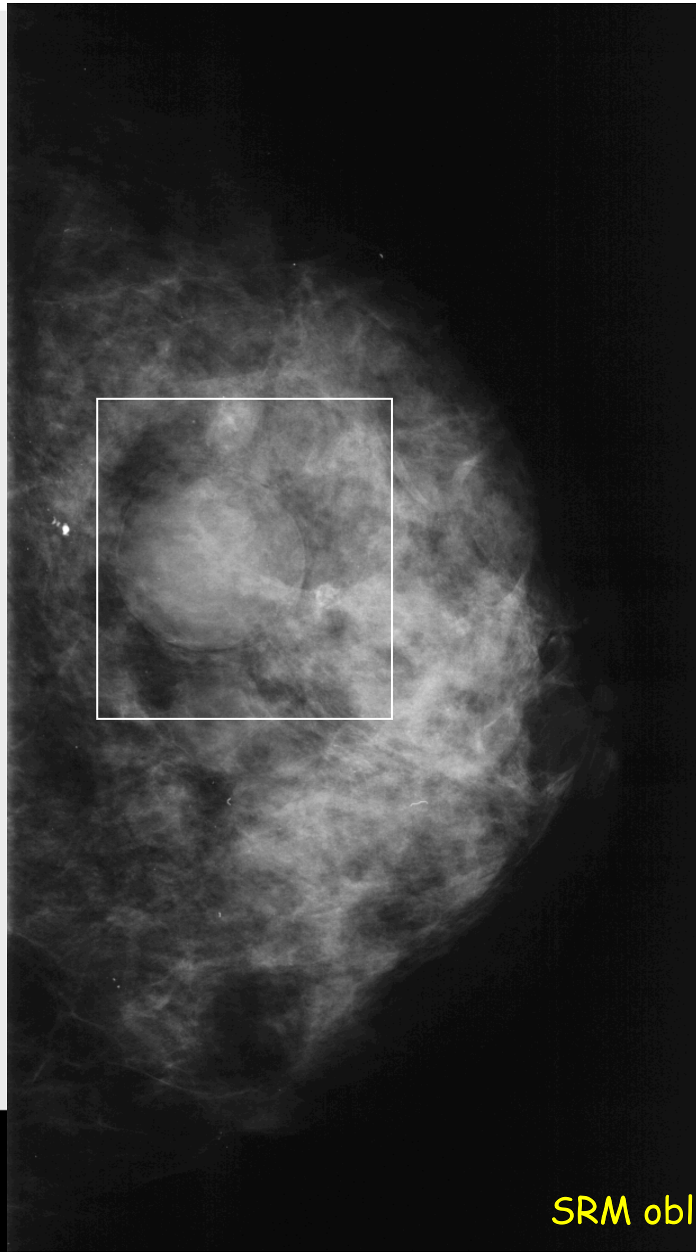
SRM: findings



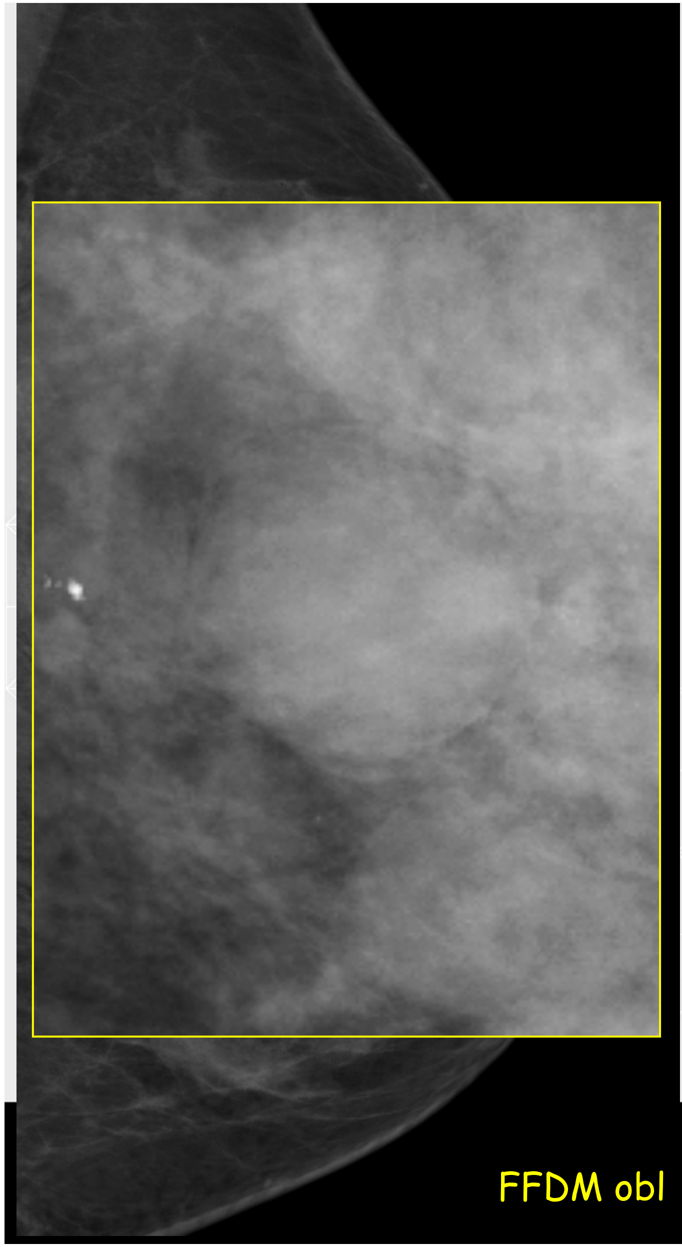


SRM: findings

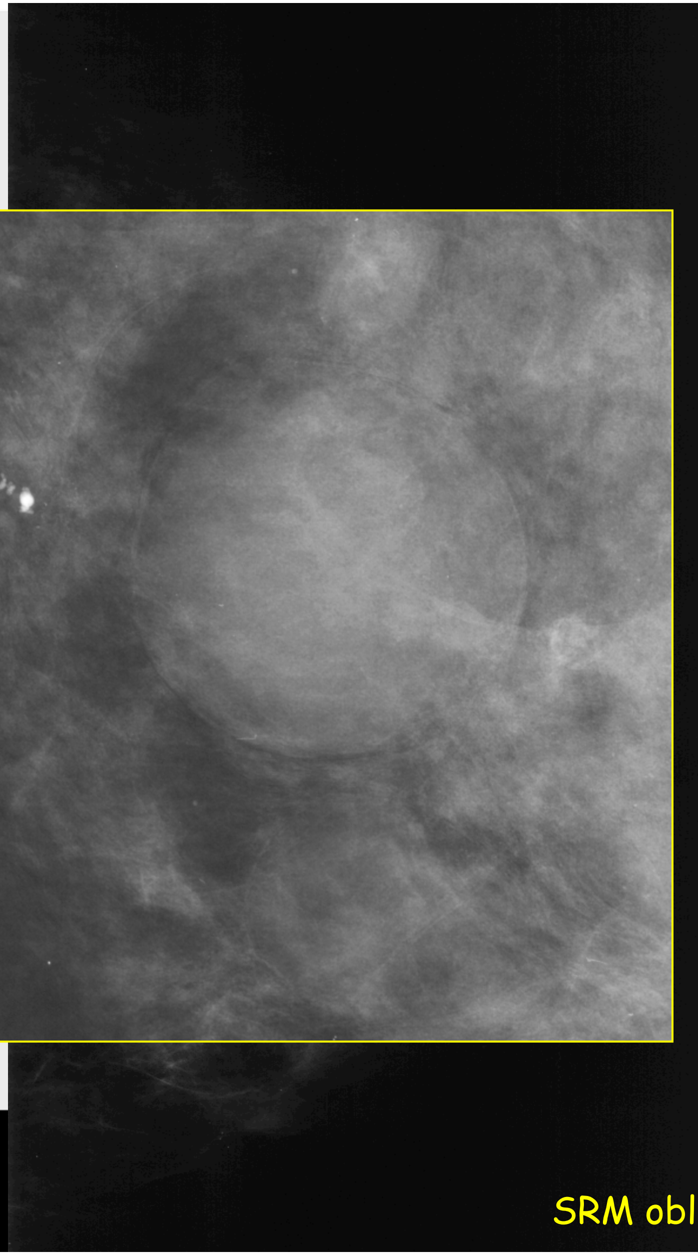




SRM: findings



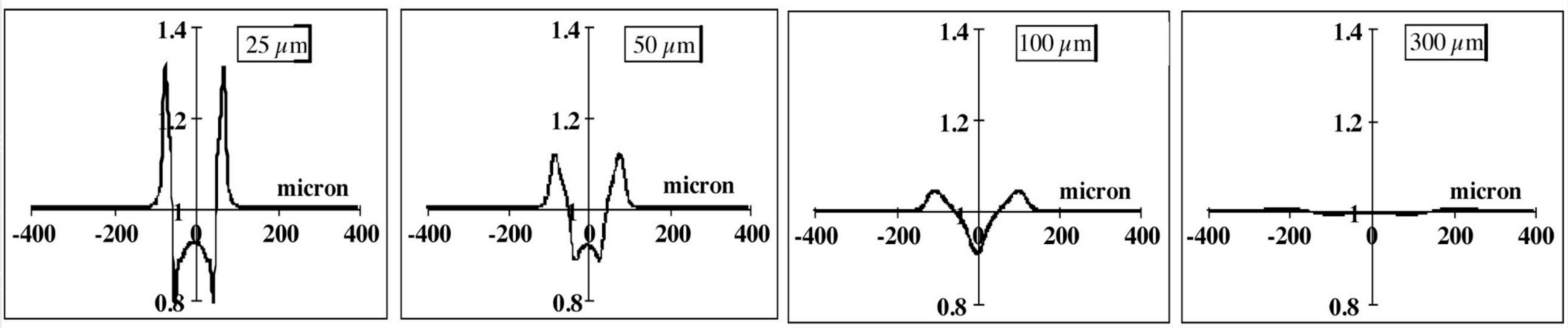
FFDM obl



SRM obl

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

- It suffer 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

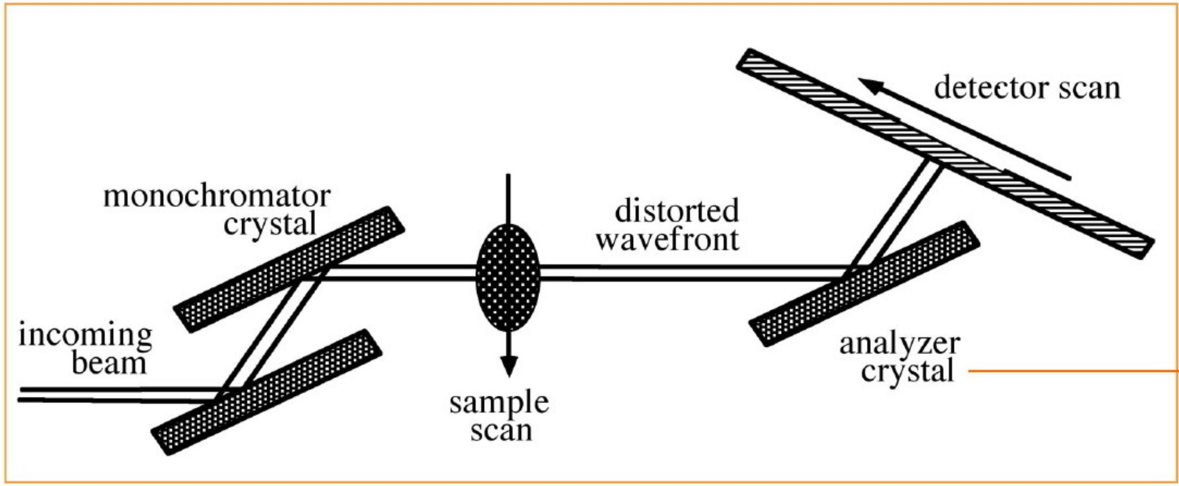
But:

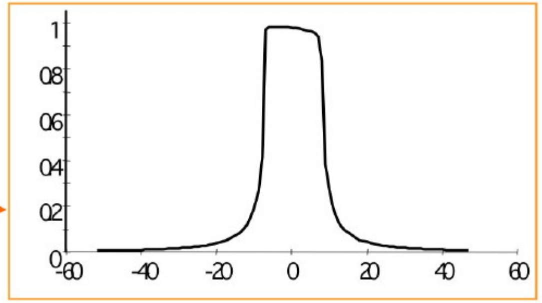
Amazing stuff @ synchrotrons, e.g. check out Cloetens' work at the ESRF
+ straightforward use e.g. coupled with Paganin's single distance phase retrieval

Olivo *et al.* Med. Phys. 28 (2001)1610-19

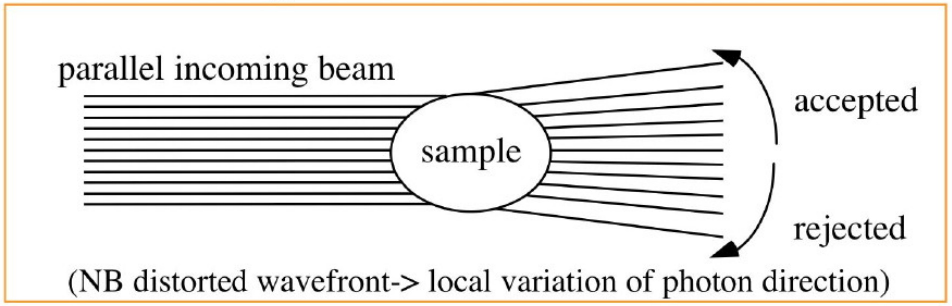
Other methods to perform phase contrast imaging:

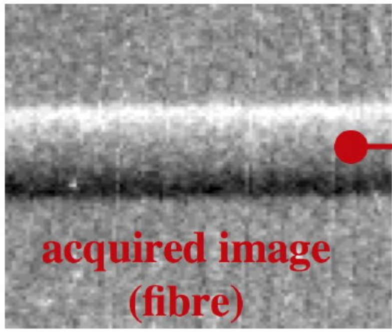
"Analyzer Based Imaging" (ABI)





a small misalignment makes it more sensitive:

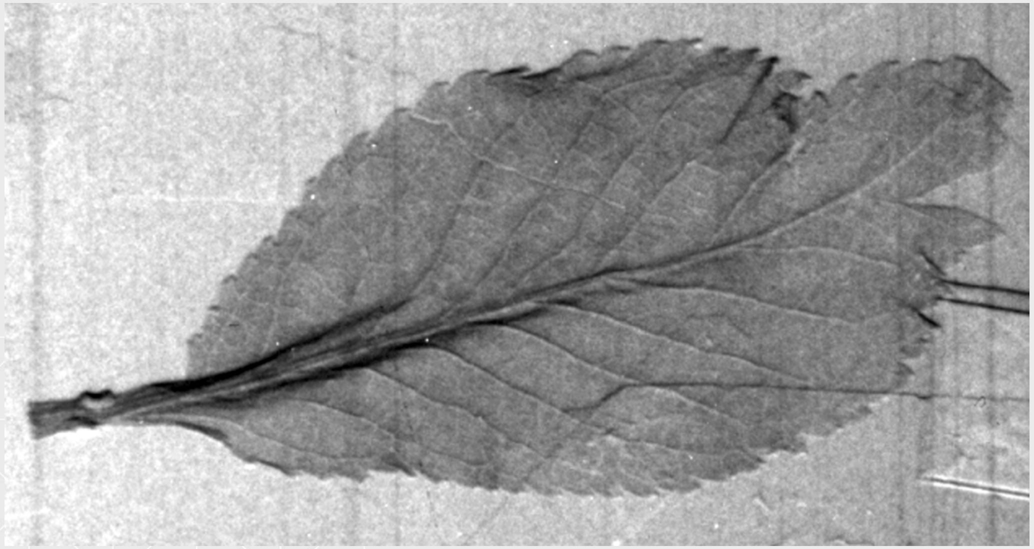




NOTE: NO ABSORPTION

Davis et al, Nature 373 (1995) 595-8; Ingal & Beliaevskaya, J. Phys. D 28 (1995) 2314-7, Chapman *et al*, Phys. Med. Biol. **42** (1997) 2015-25 - **but even before that Forster 1980!**

ABI produces TERRIFIC image quality:



BUT:

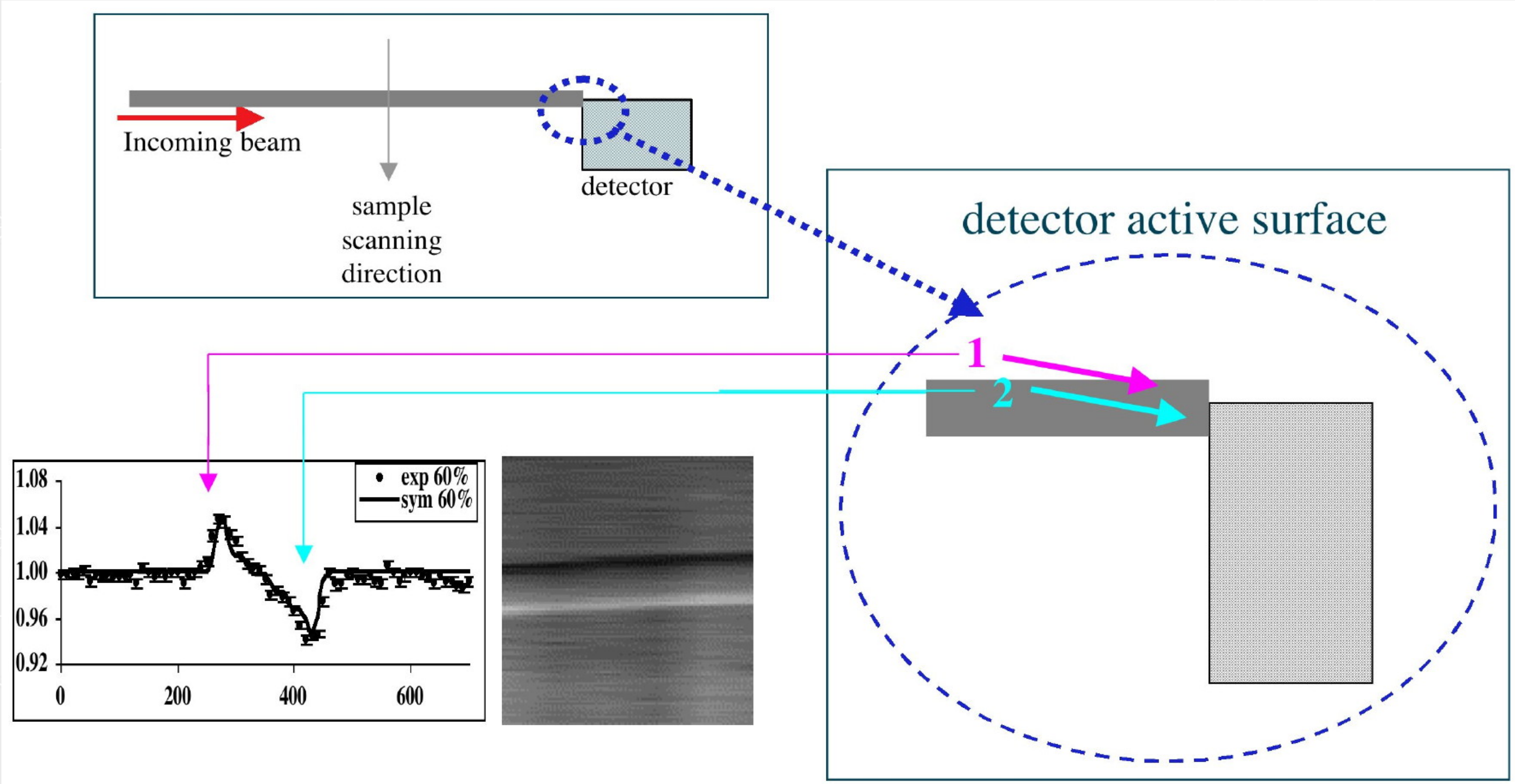
- **x-rays must be parallel and monochromatic**

if they aren't, that's what left of the beam after it goes through the crystal

- **you are again confined to synchrotrons,** or to very long exposure times.

A different way to obtain a similar effect:

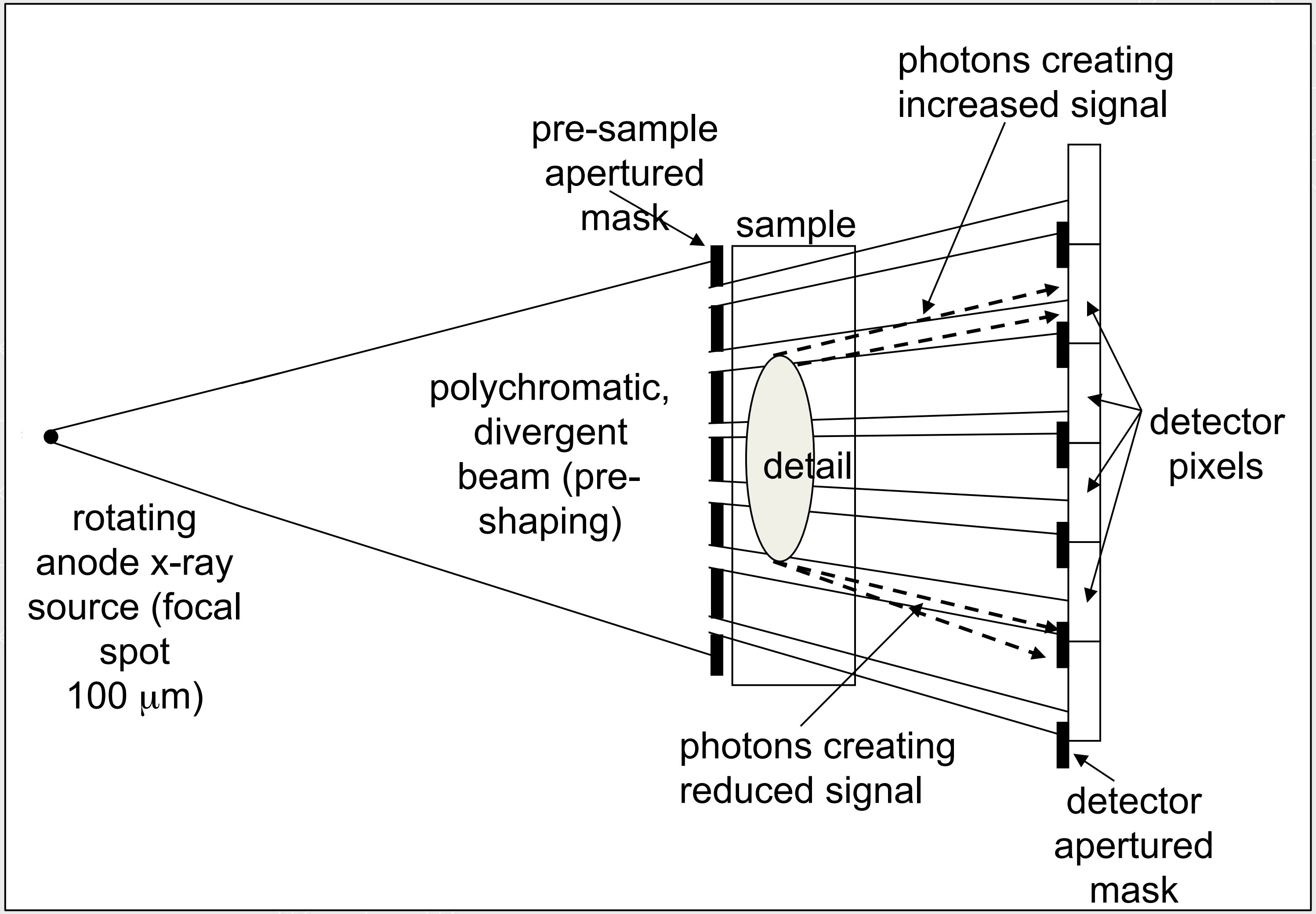
The Edge Illumination Technique



Provides results similar to ABI but opens the way to the use of **__divergent__ and __polychromatic__ beams**

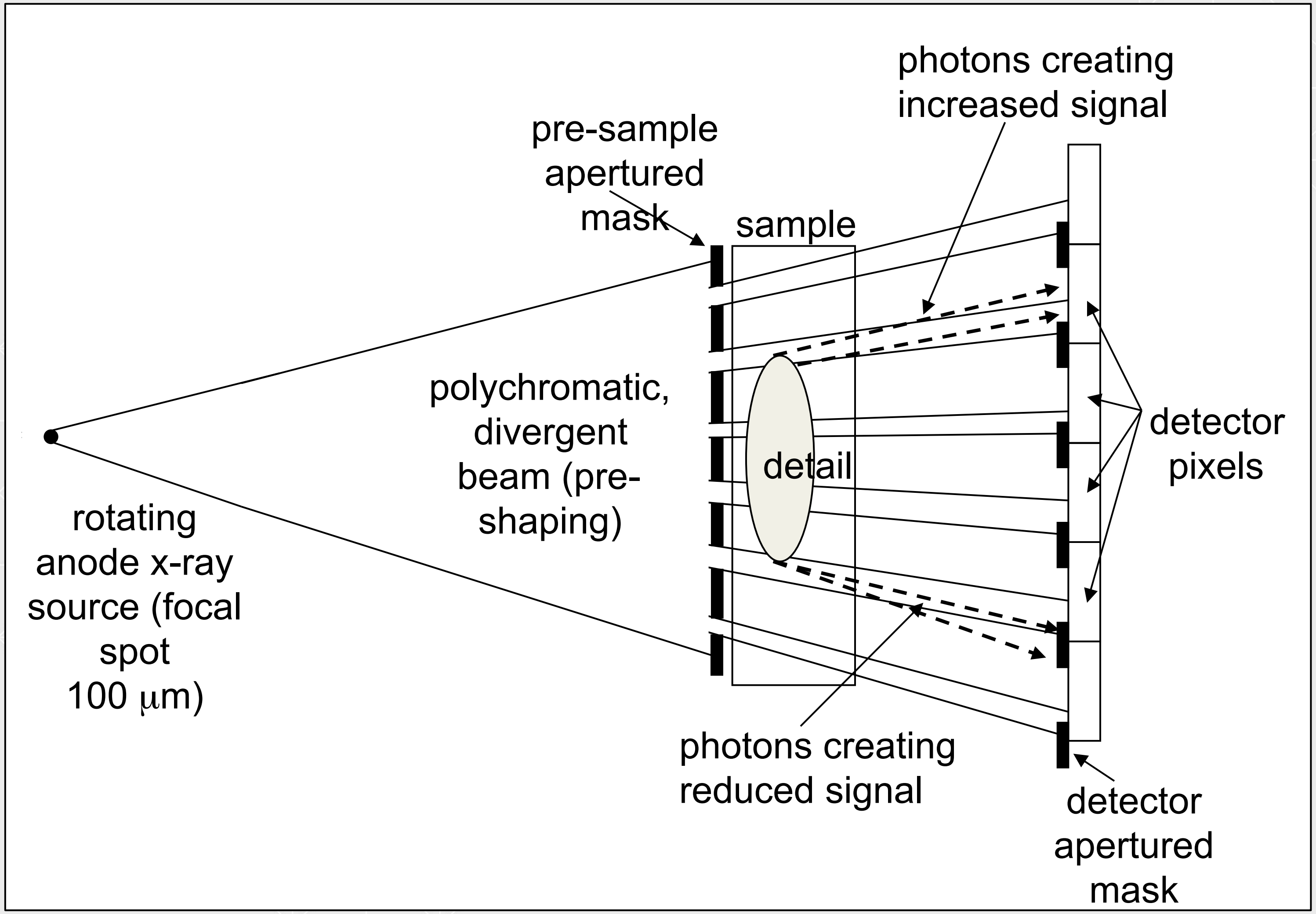
Olivo *et al.* Med. Phys. 28 (2001)1610-19

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



Olivo and Speller Appl. Phys. Lett. 91 (2007) 074106

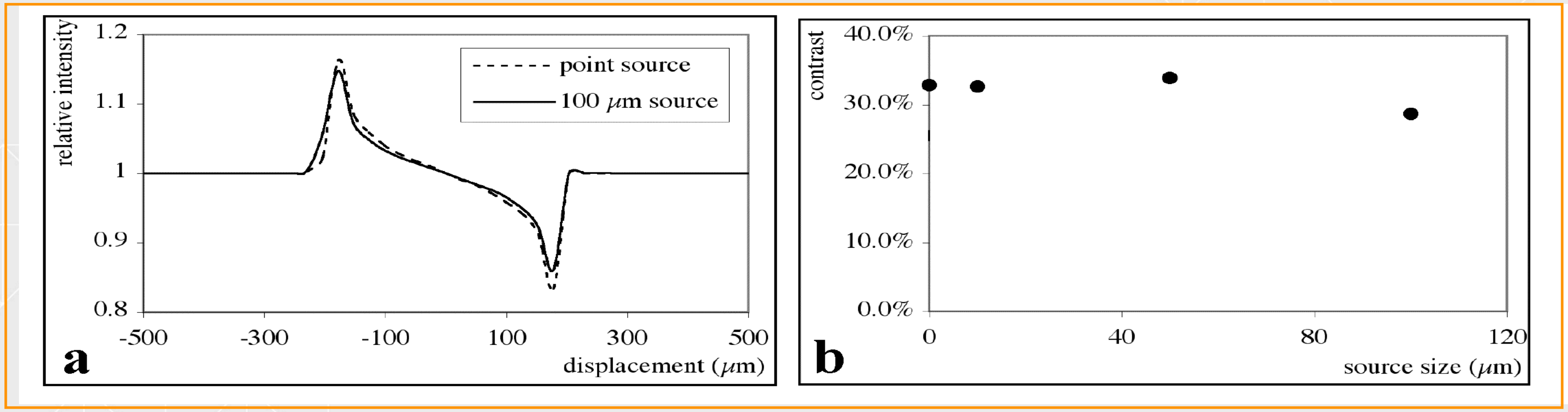
THE METHOD CAN BE ADAPTED TO A DIVERGENT AND POLYCHROMATIC (=conventional) SOURCE



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

Olivo and Speller Appl. Phys. Lett. 91 (2007) 074106

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



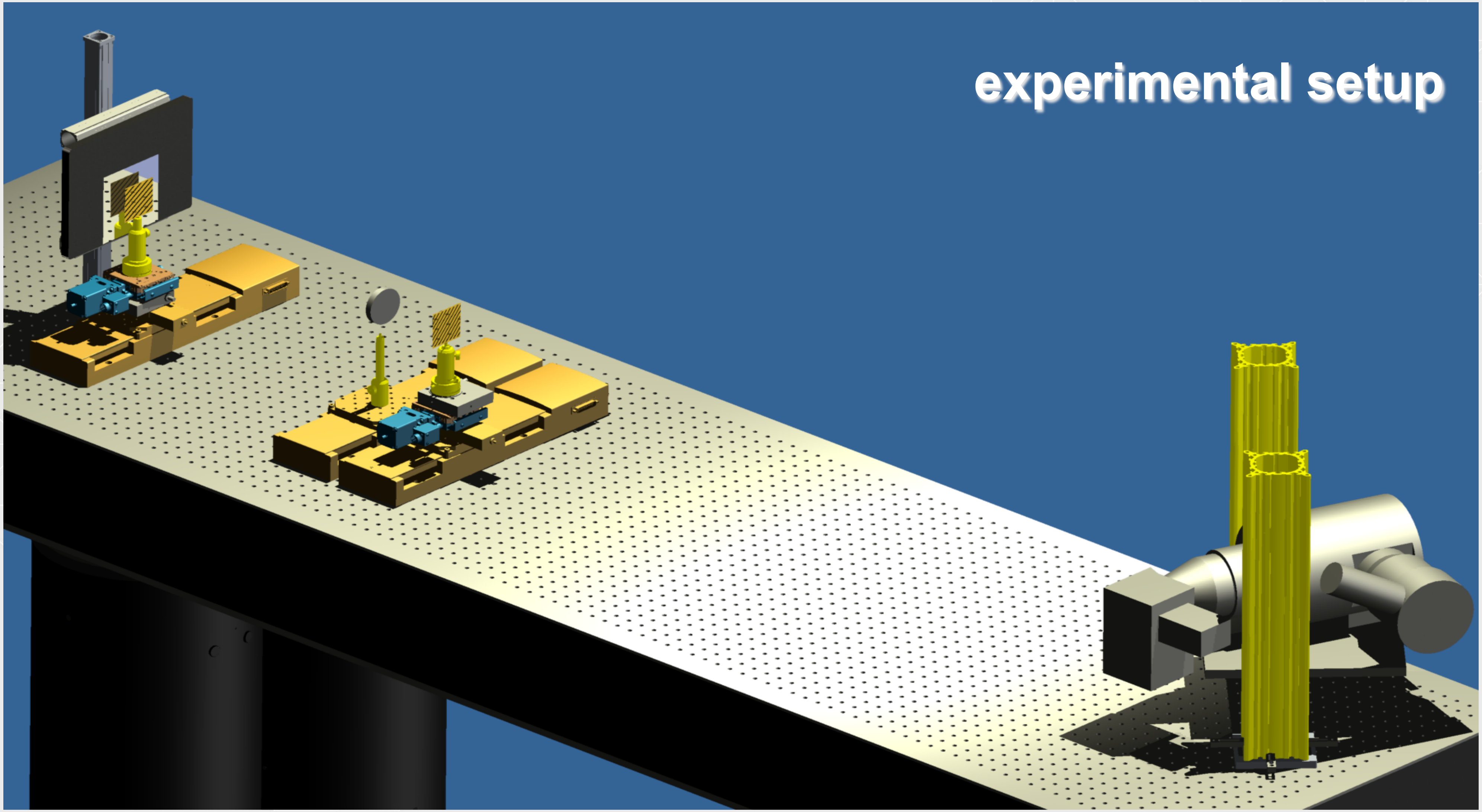
Which can be achieved with state-of-the-art mammo sources

Why?

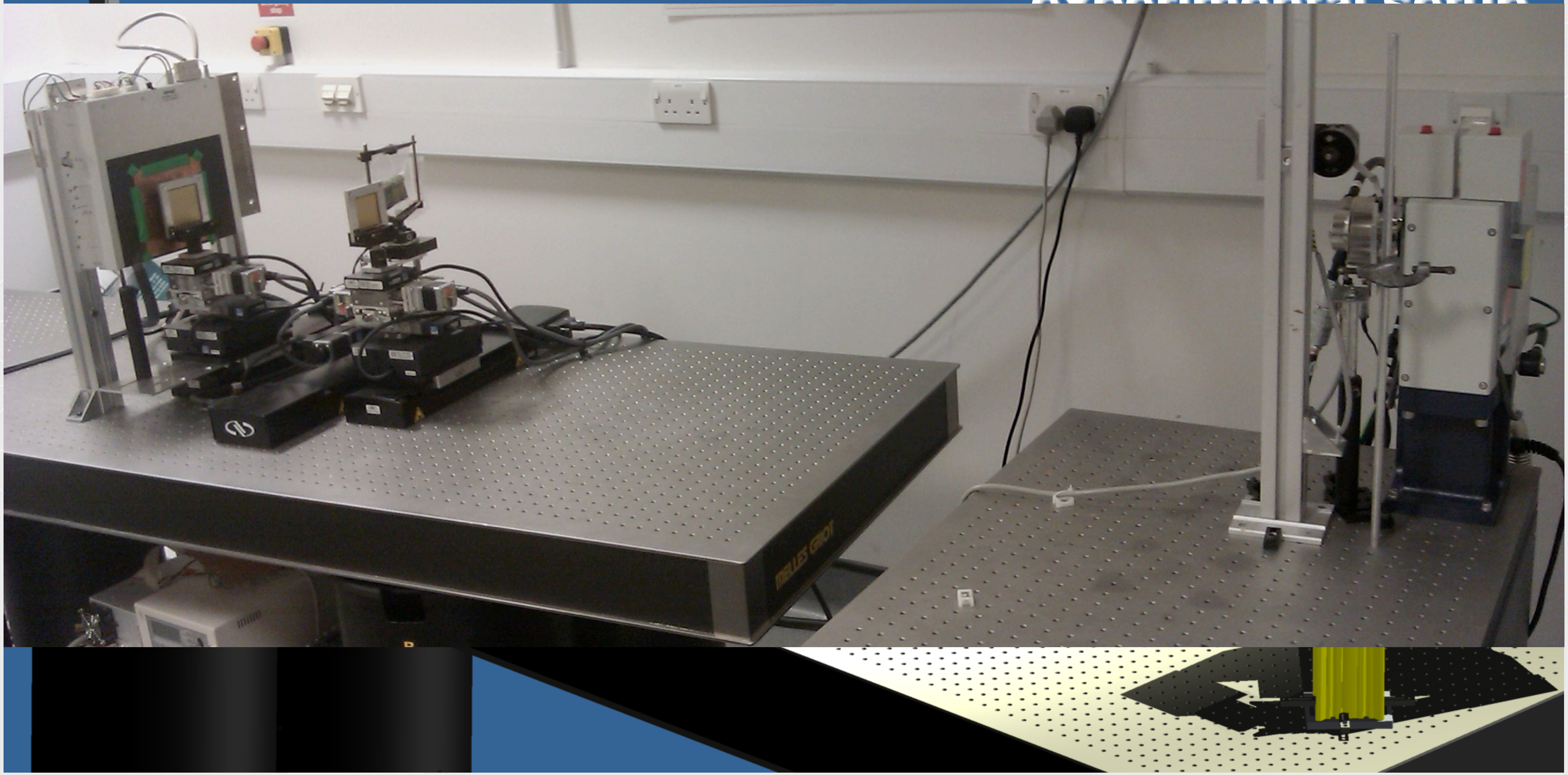
1) Because we are only relying on refraction, which survives under relaxed coherence conditions;
2) Because we are use aperture pitches matching the pixel size, i.e. BIG: the projected source size remains < pitch, and therefore blurring does "not" occur.

Olivo and Speller Phys. Med. Biol. 52 (2007) 6555-73

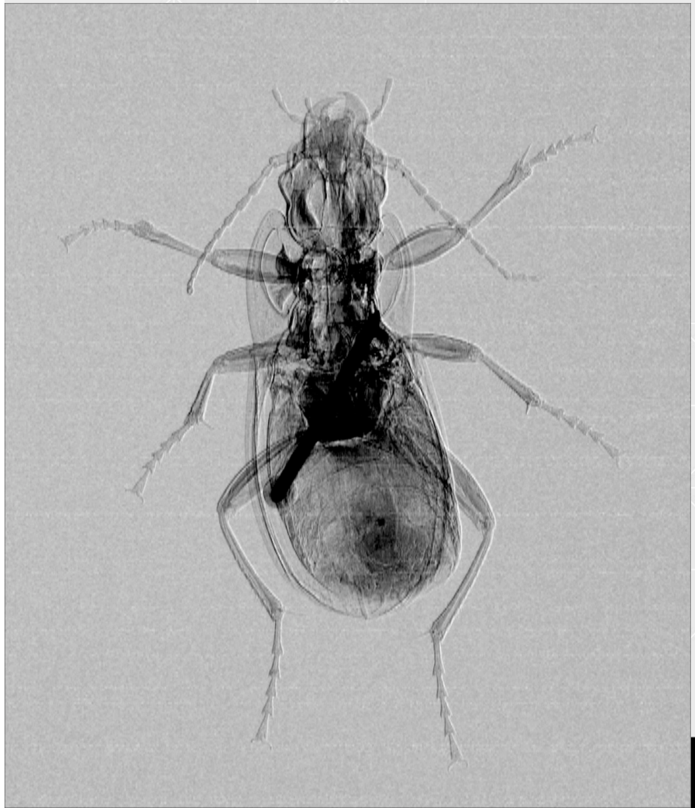
experimental setup



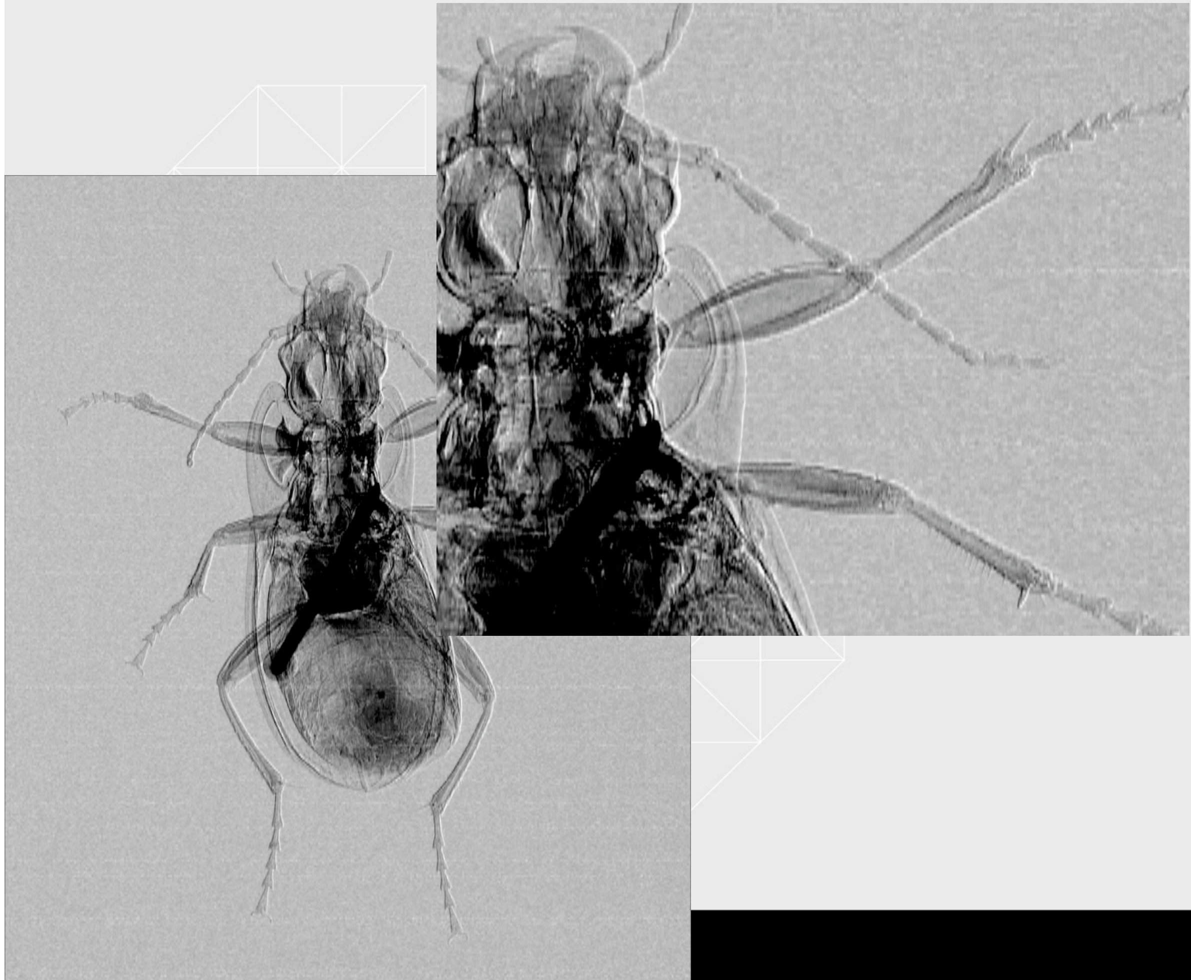
experimental setup



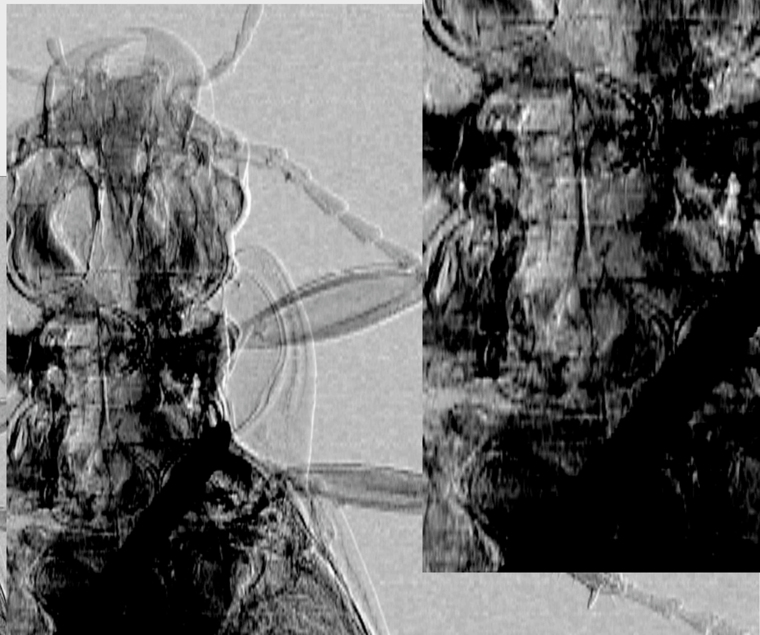
Preliminary results: the “usual” insects (but a bit faster)

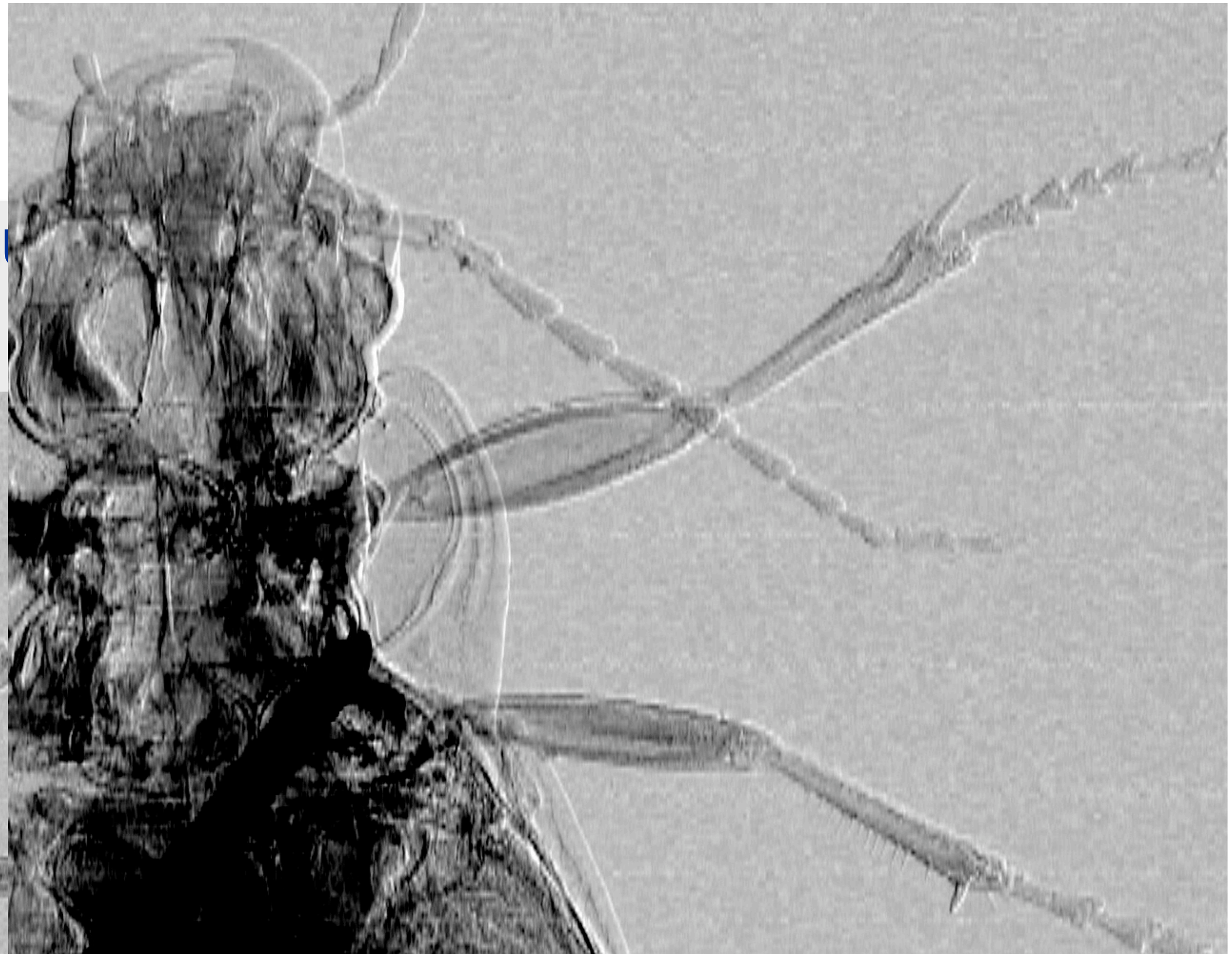


Preliminary results: the “usual” insects (but a bit faster)



Preliminary results: the “usu





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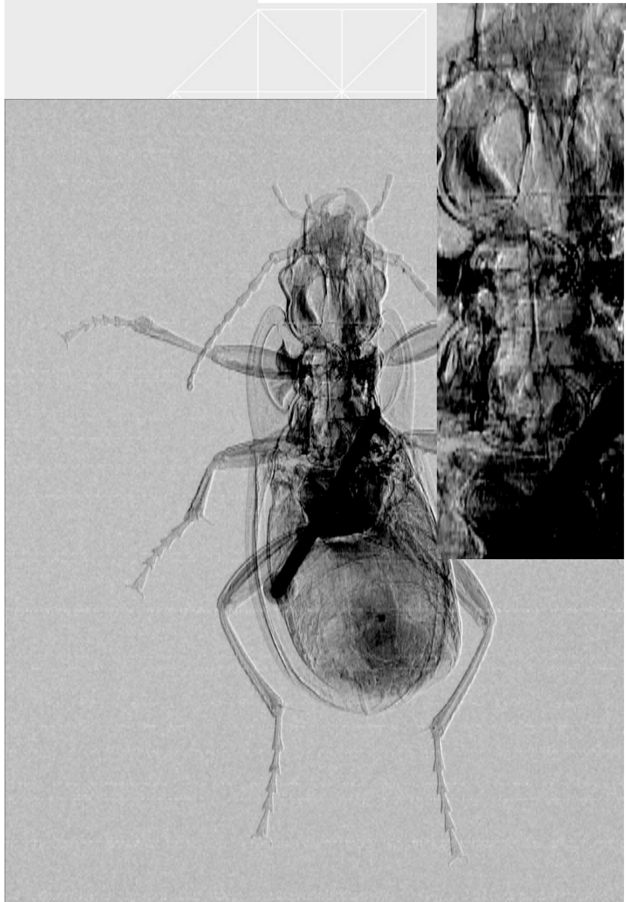
Research Complex at Harwell

Prelimir

RESEARCH HIGHLIGHTS Selections from the scientific literature



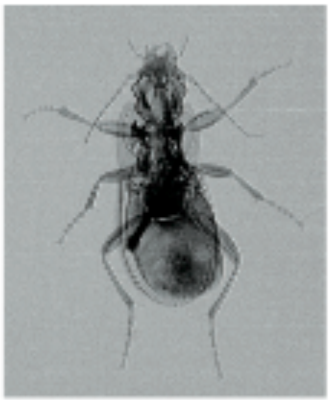
APPLIED PHYSICS

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.

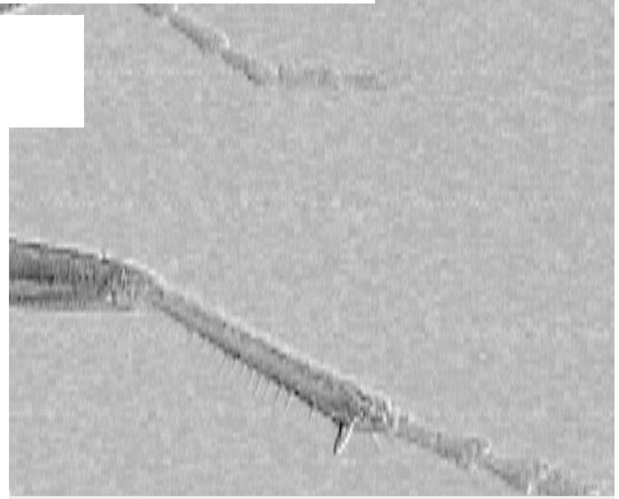
A. OLIVO ET AL.



Alessandro Olivo and his colleagues at University College London used a conventional X-ray source outfitted with grated 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)



IBME UCL Institute of Biomedical Engineering

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Nature 472 (2011) p. 392

ADVANCES

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 grates that are 100 microns or so thick—one in front of a target and one behind it. The holes on one grate do not line up exactly with the holes on the other, meaning x-rays that passed in straight lines through the first grate 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 grating 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 scanning, 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

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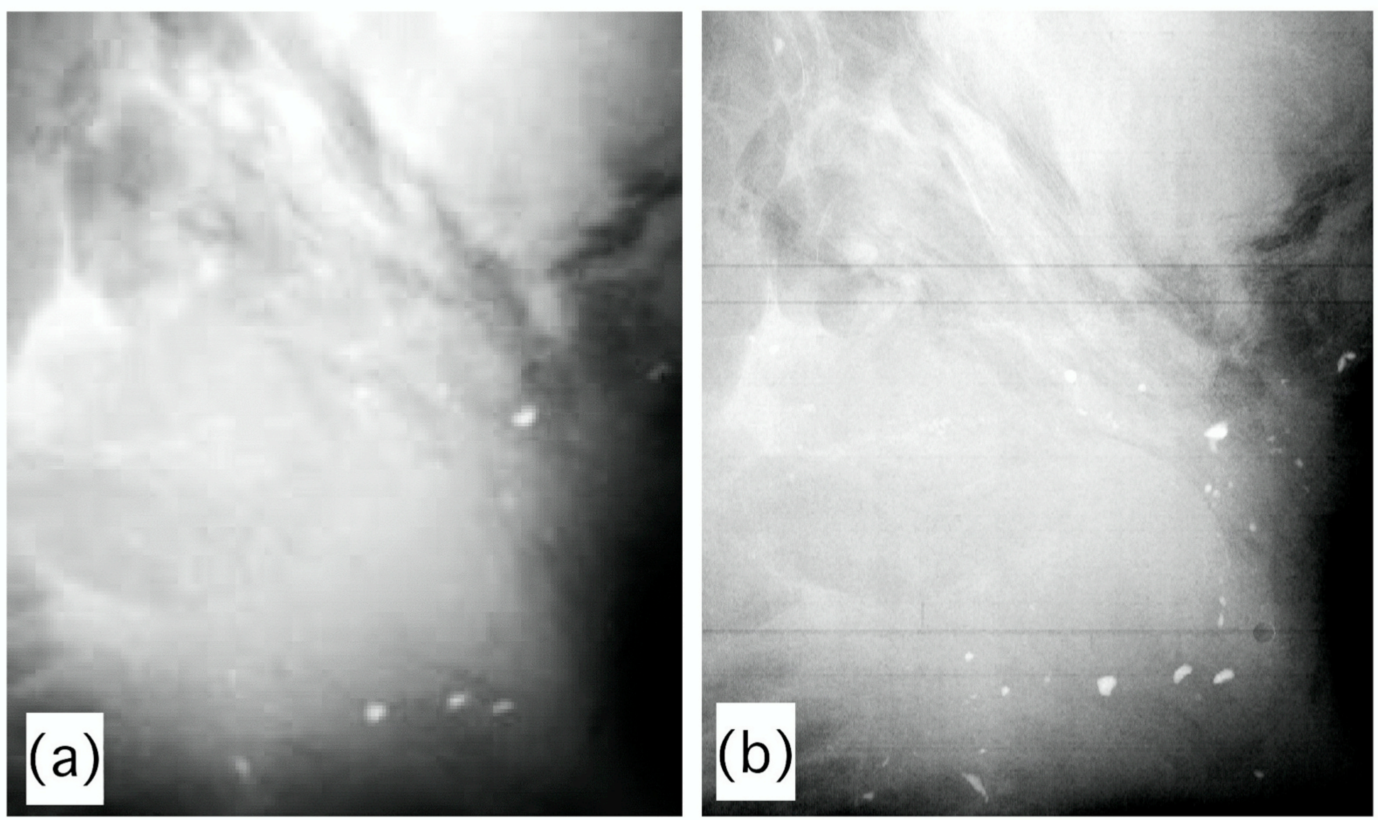
Preliminary results - mammo



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

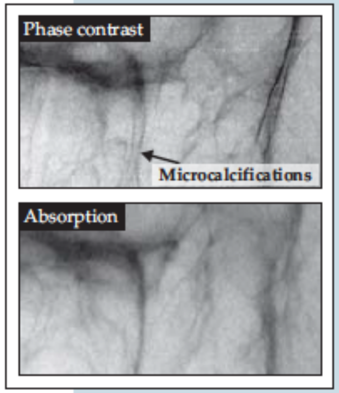
(b): coded-aperture XPCi, 40 kVp, 25 mA – **ENTRANCE** dose 7 mGy (< mammo!)

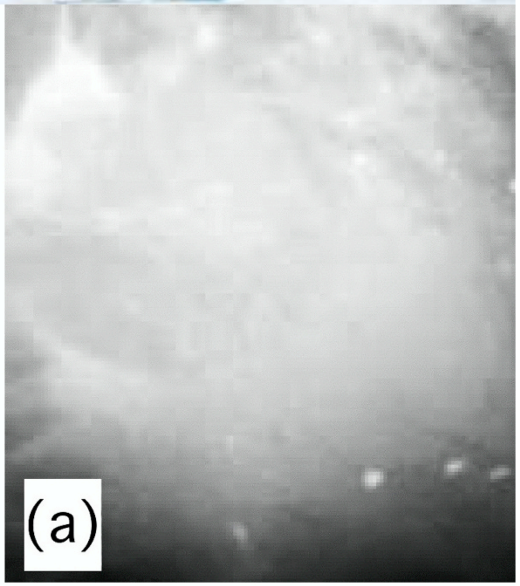
It has to be said the tissue was 2.5 cm thick -> we expect ~ same dose for thicker tissues

Olivo et al Med. Phys. (letters) 40 (2013) 090701

www.physicstoday.org
physics today
A publication of the American Institute of Physics
October 2013 volume 66, number 10

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





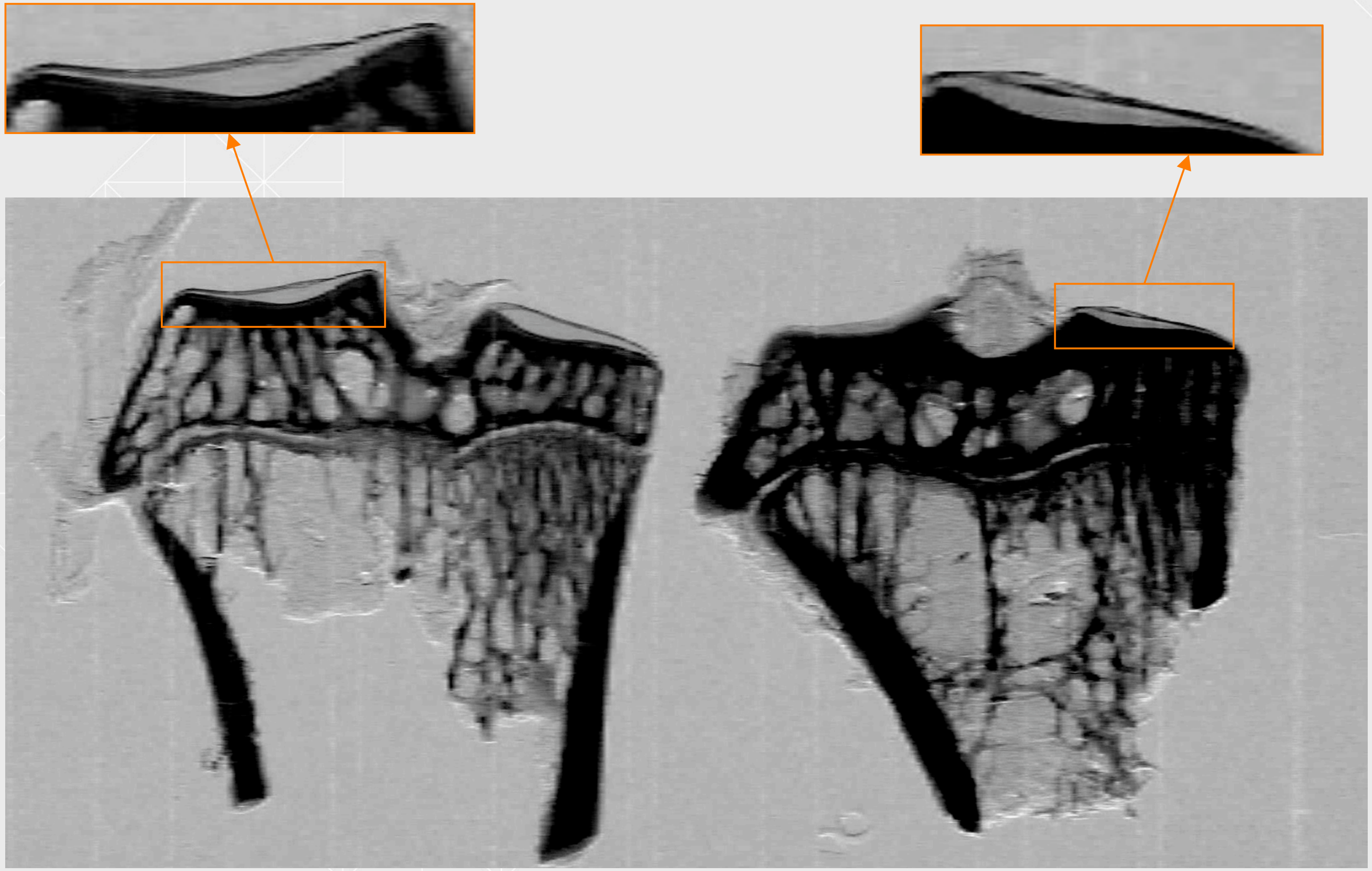
(a): GE senographe Essential AD

(b): coded-aperture XPCi, 40 kVp ... < mammo!)

It has to be said the tissue was 2.5 cm th... s

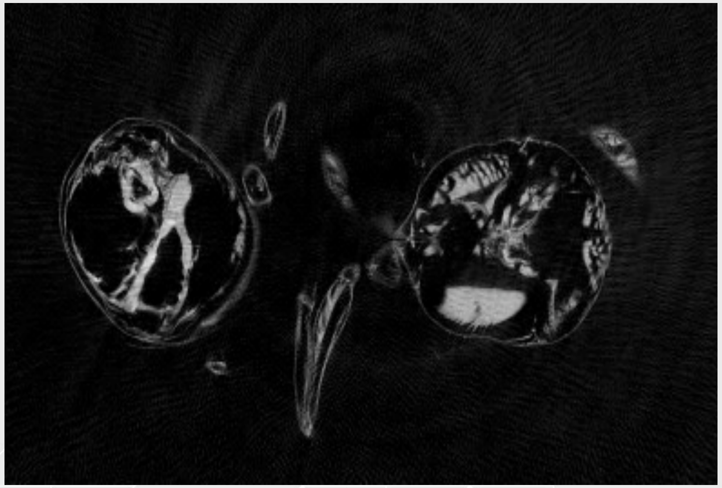
Preliminary results - cartilage imaging

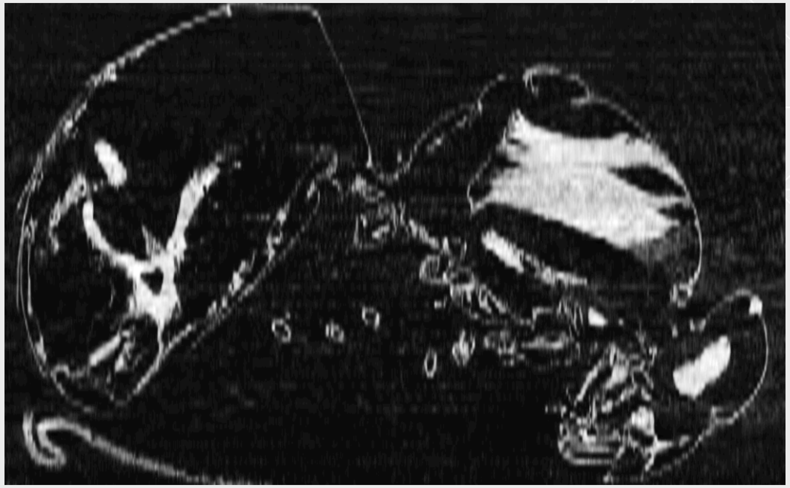
Rat cartilage, ~ 100 μm thick, invisible to conventional x-rays

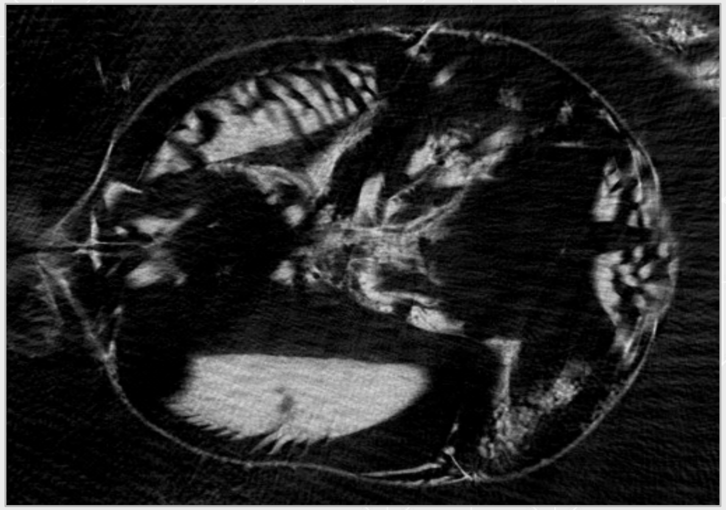


Marenzana *et al*, Phys. Med. Biol. 57 (2012) 8173-84

Early CT results







Soft tissue inside wasp thorax resolved

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

Hagen et al, Med. Phys. (letters) 41 (2014) 070701

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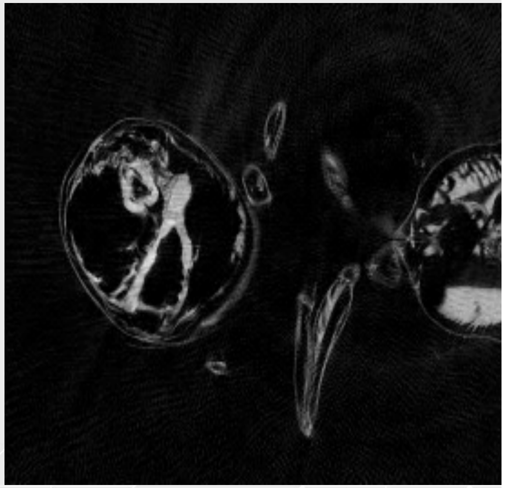
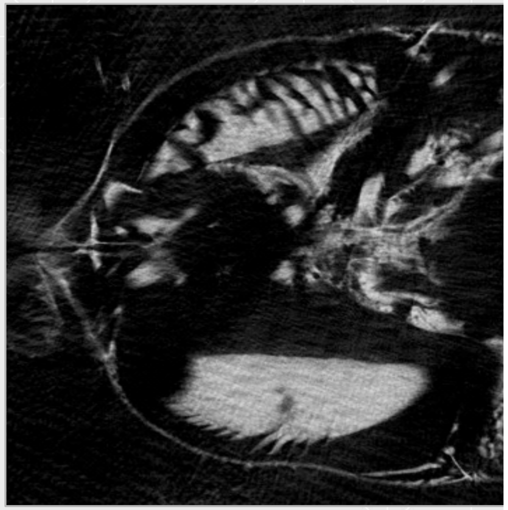
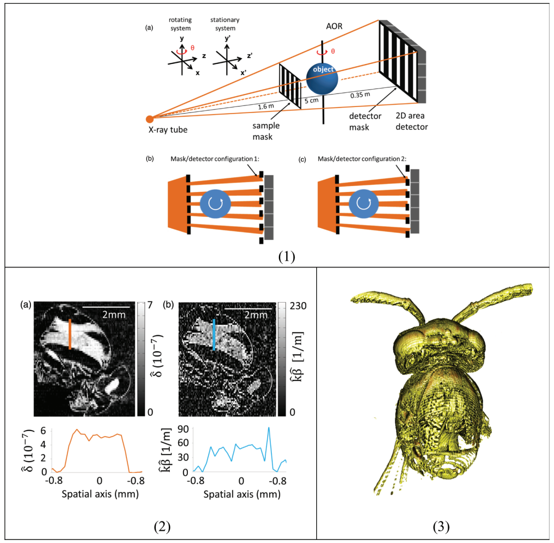
Medical Physics

AVAILABLE ONLINE—See http://www.medphys.org July 2014 Volume 41, Number 7

The International Journal of Medical Physics Research and Practice







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 Olivo, "Low-dose phase contrast tomography with conventional x-ray sources," Med. Phys. 41, 070701 (5pp.) (2014)].

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.**

Hagen et al, Med. Phys. (lett

Soft tissue inside wasp thorax resolved

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

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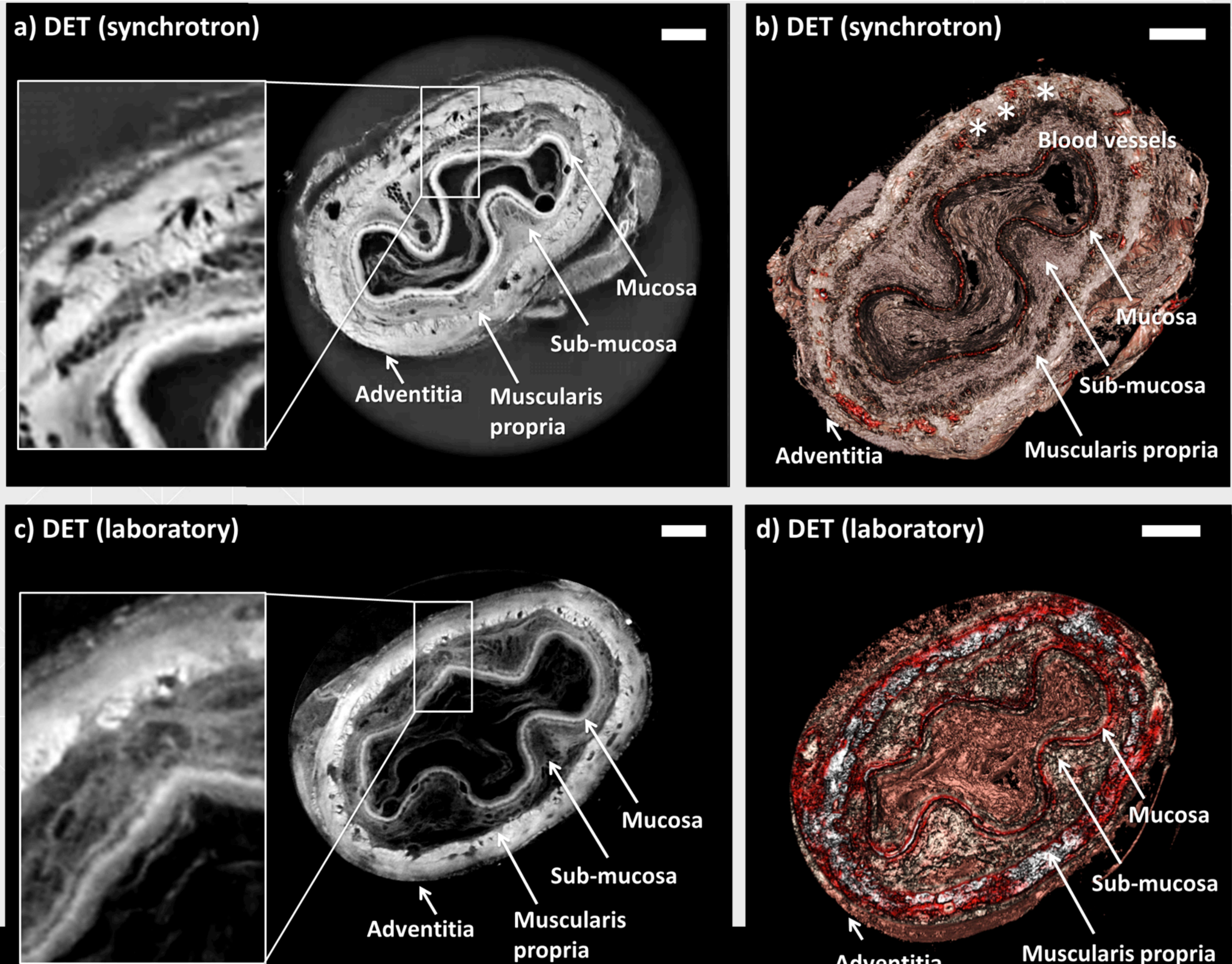
First CT results

another example, fully decellularized tissue

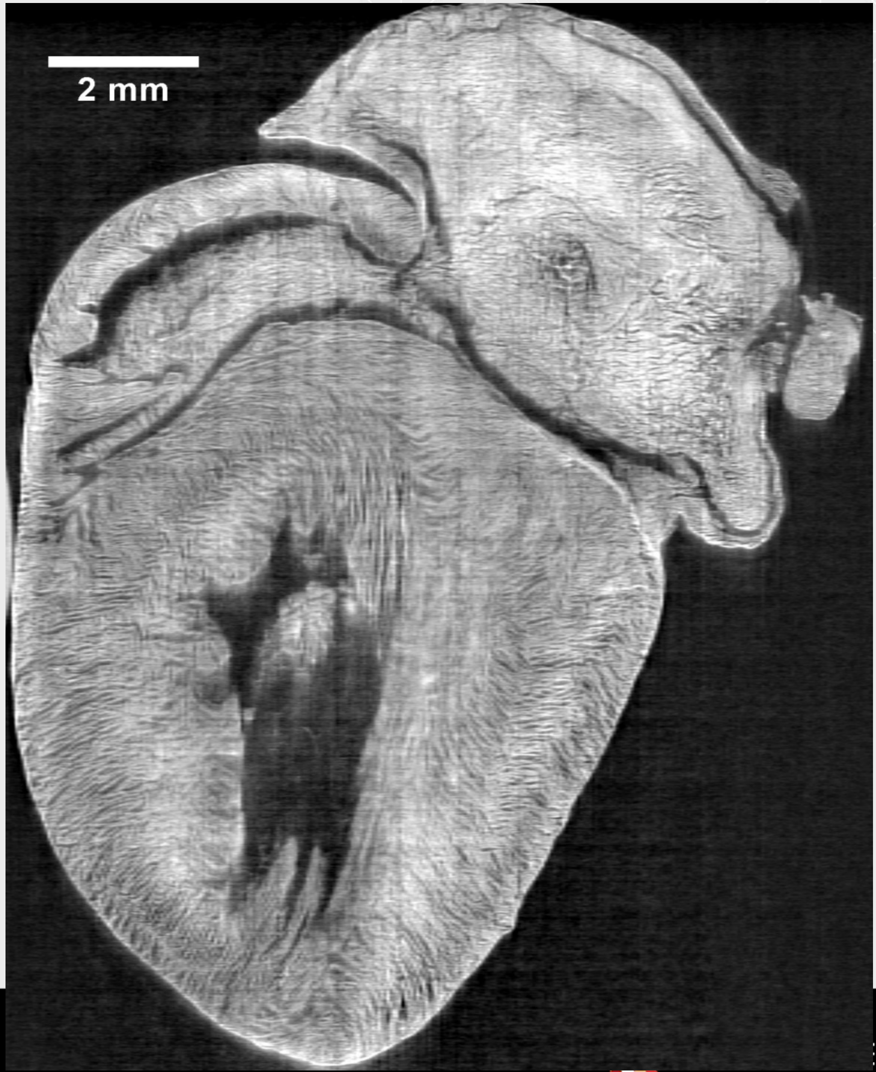


Hagen *et al*, Sci. Rep. 5 (2015) 18156

Rat heart

axial

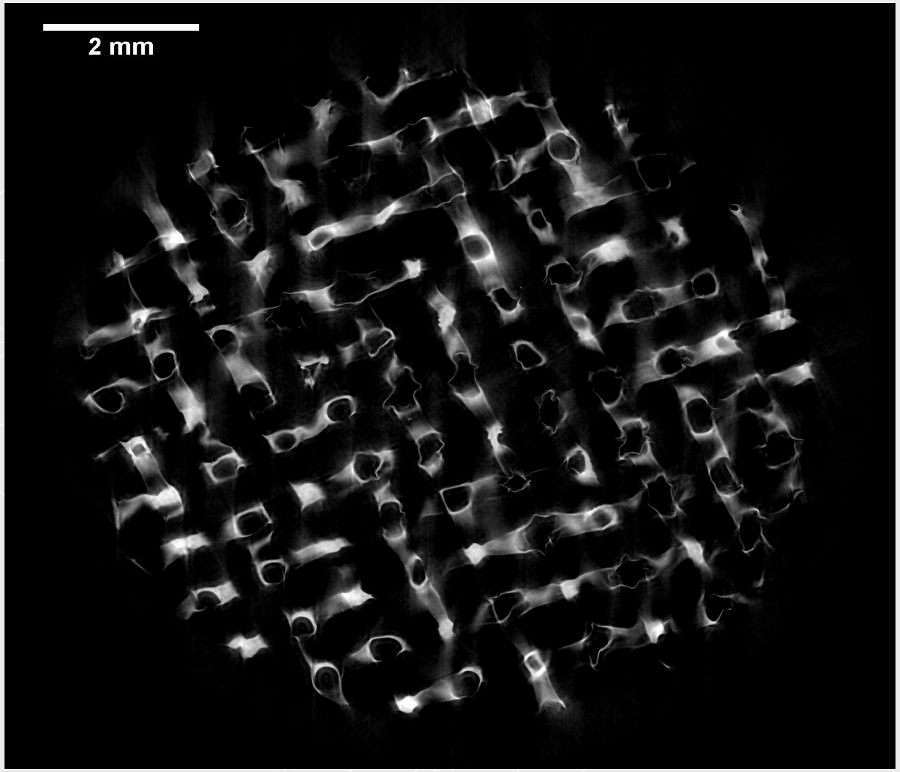
reslice



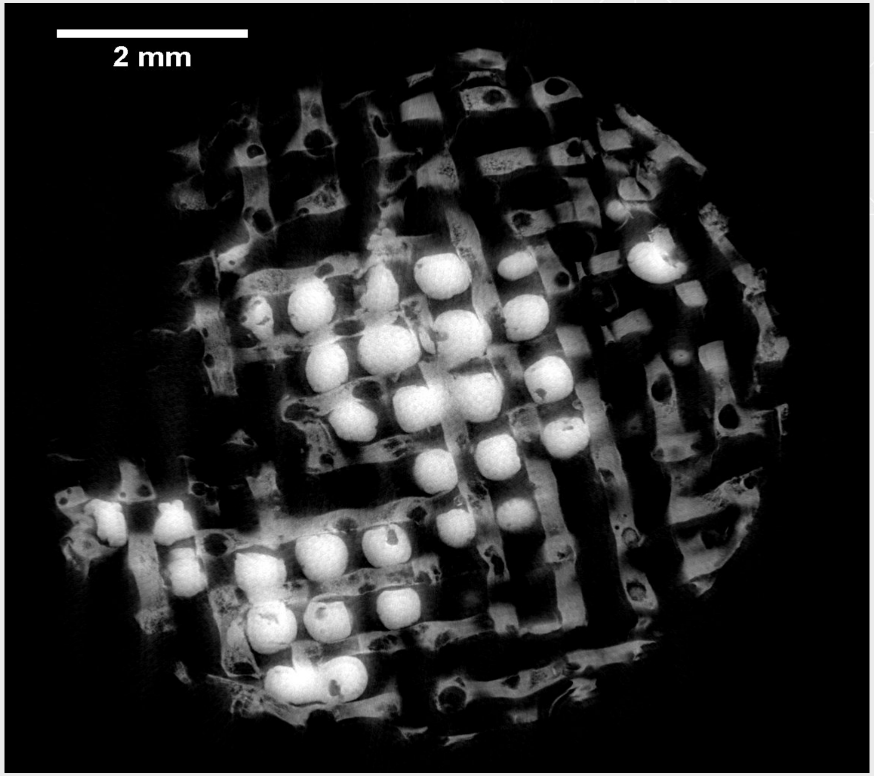
Zamir et al, Sci. Rep. 6 (2016) 31197

3D-printed scaffolds

No cells



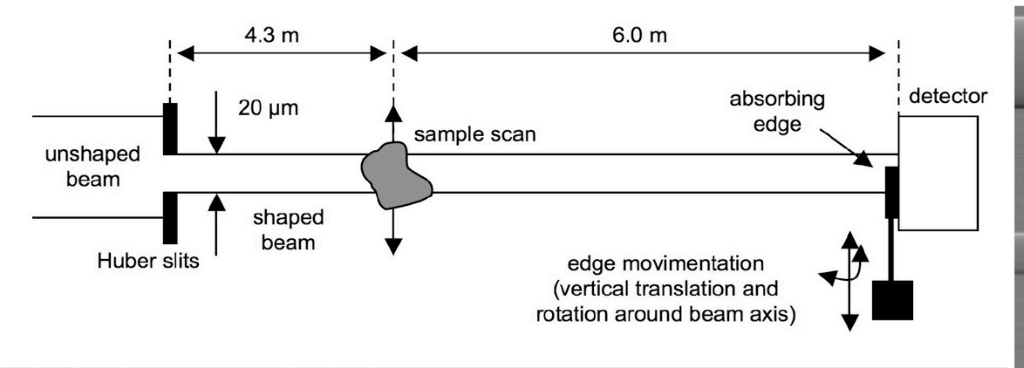
Cells (7 days after seeding)

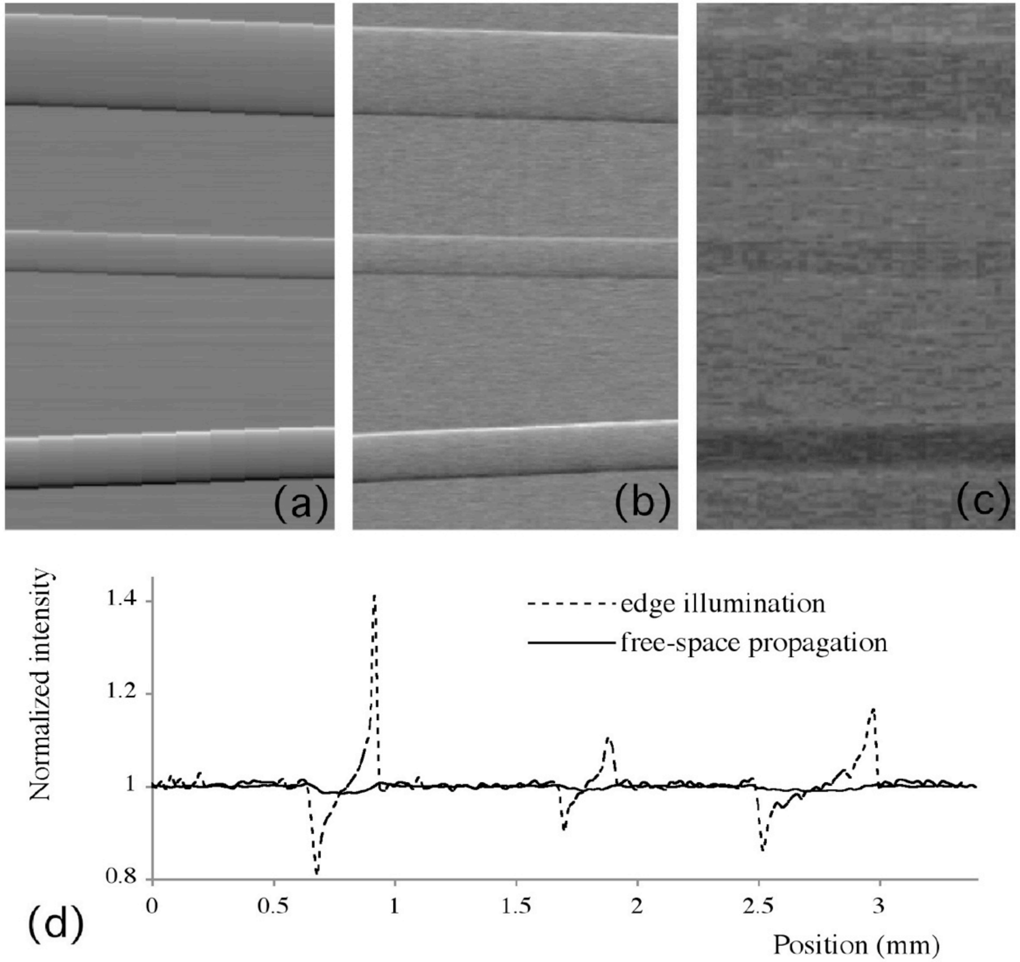


Unpublished

Even higher (monochromatic) energy - ESRF, 85 keV

very simple set-up… -> highly increased contrast!





Olivo *et al*, Opt. Lett. 37 (2012) 915-7

Even higher (monochromatic) energy - ESRF, 85 keV

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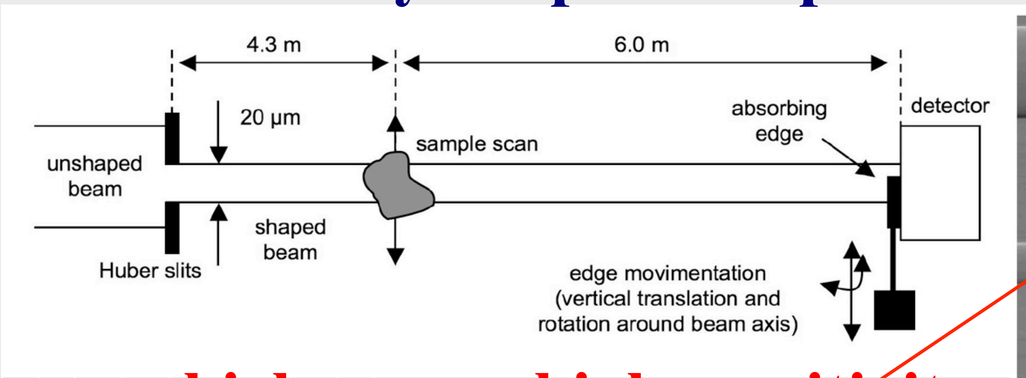
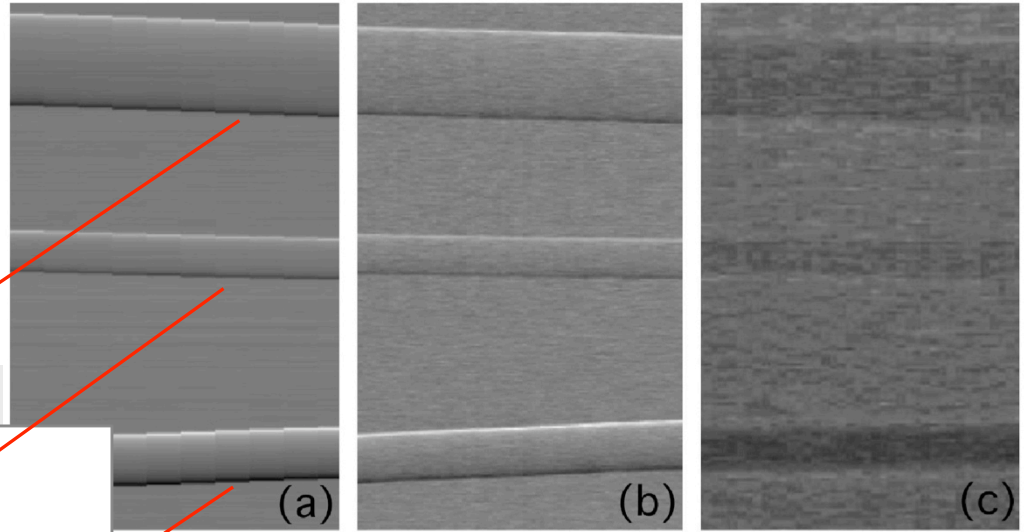
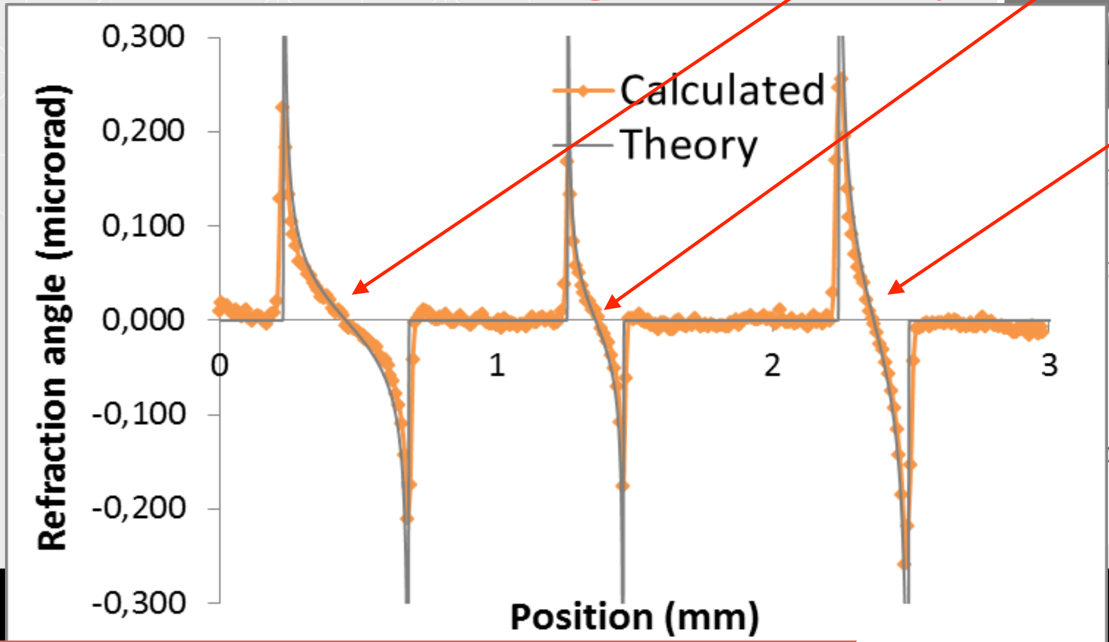
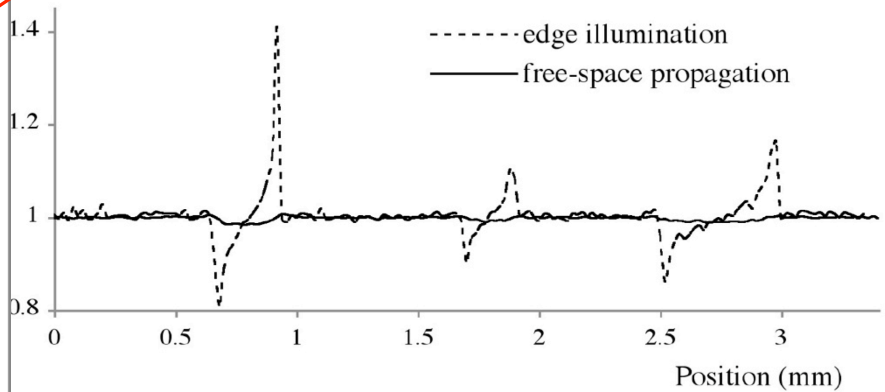


-> highly increased contrast!



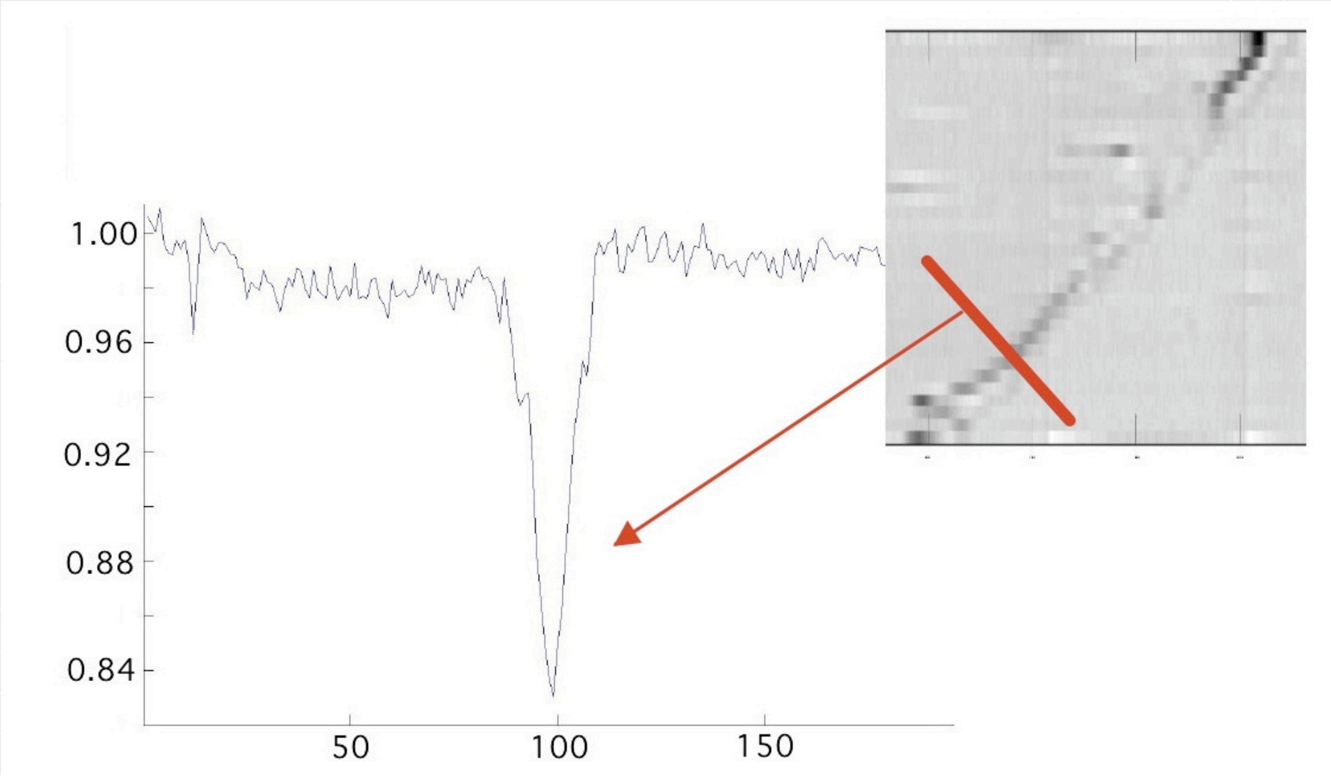
-> which means high sensitivity





Diemoz *et al*, Phys. Rev. Lett. 110 (2013) 138105

Exploitation of additional sensitivity to push the detection threshold further:

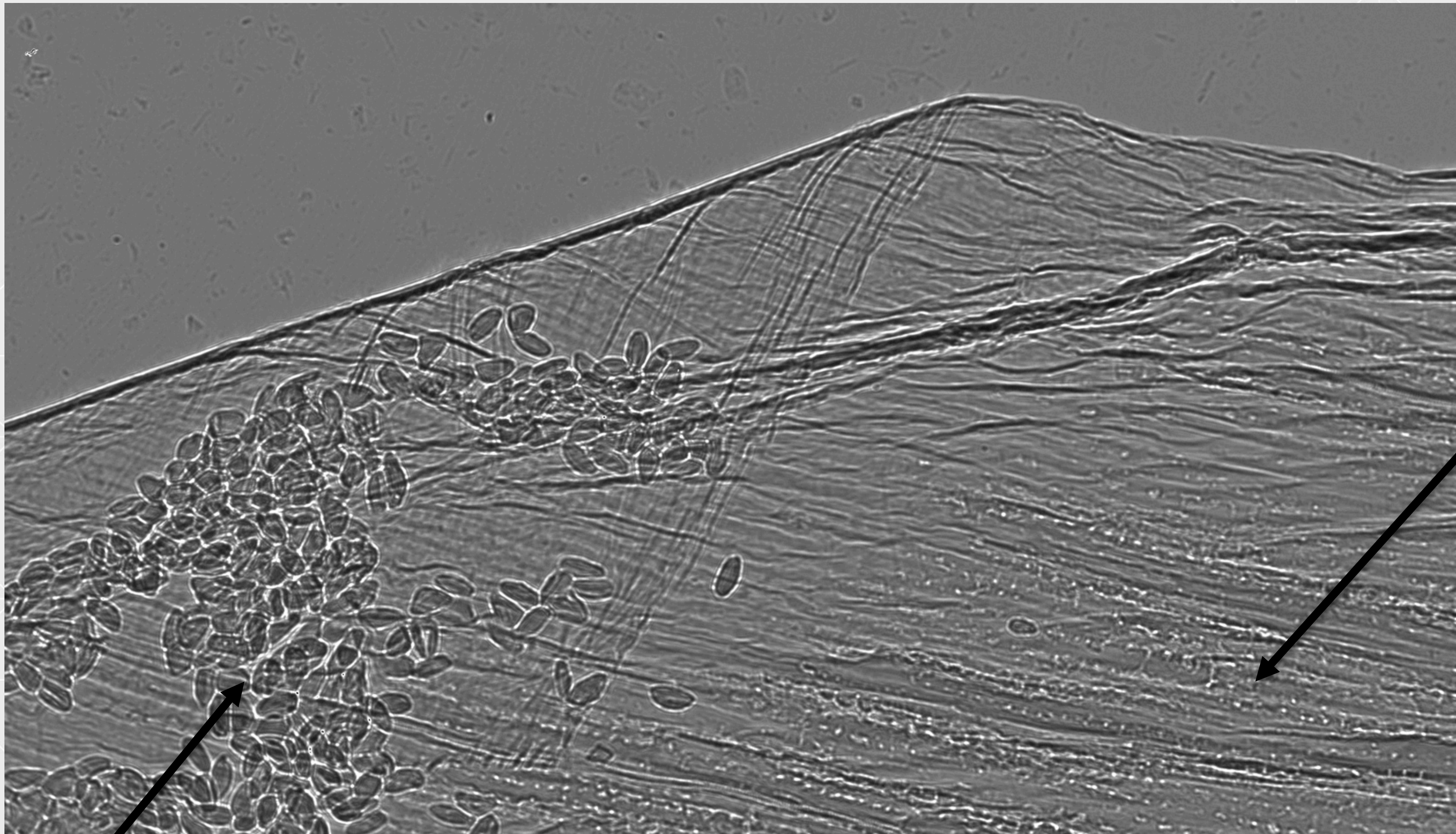


A 10 micron thick polyethilene foil immersed in water (-> matching refractive index!) generates an unprecedented **16%** image contrast!

Practically corresponds to a single cell in water

Diemoz *et al*, Phys. Rev. Lett. 110 (2013) 138105

Which of course can be generalized to other biological applications, etc

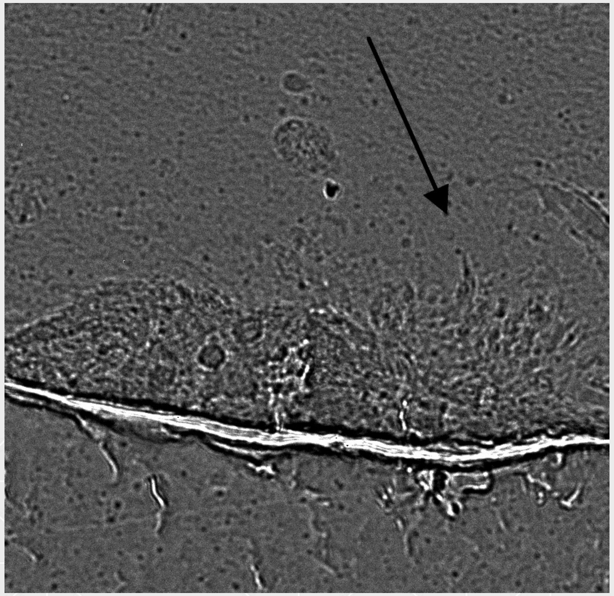


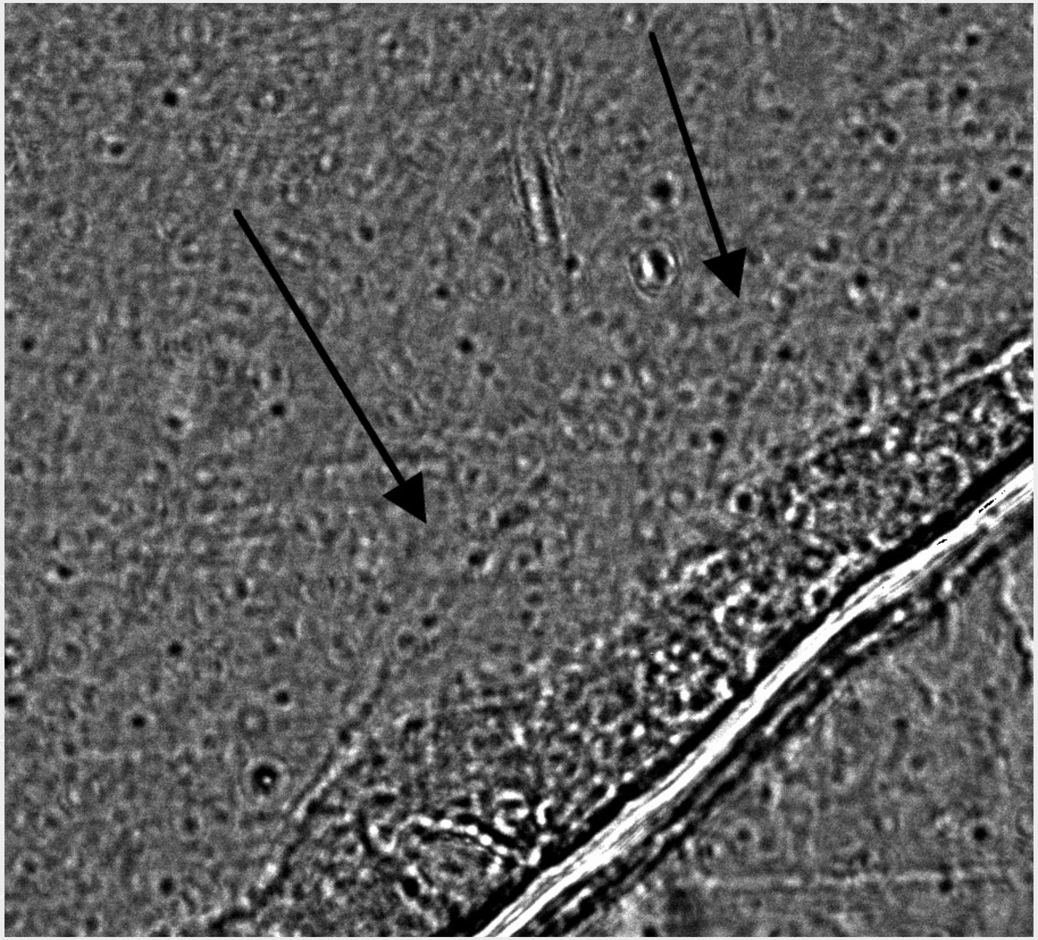
Individual lines of cells along petal veins

pollen

Diemoz et al J. Synchrotron Rad. 22 (2015) 1072-77

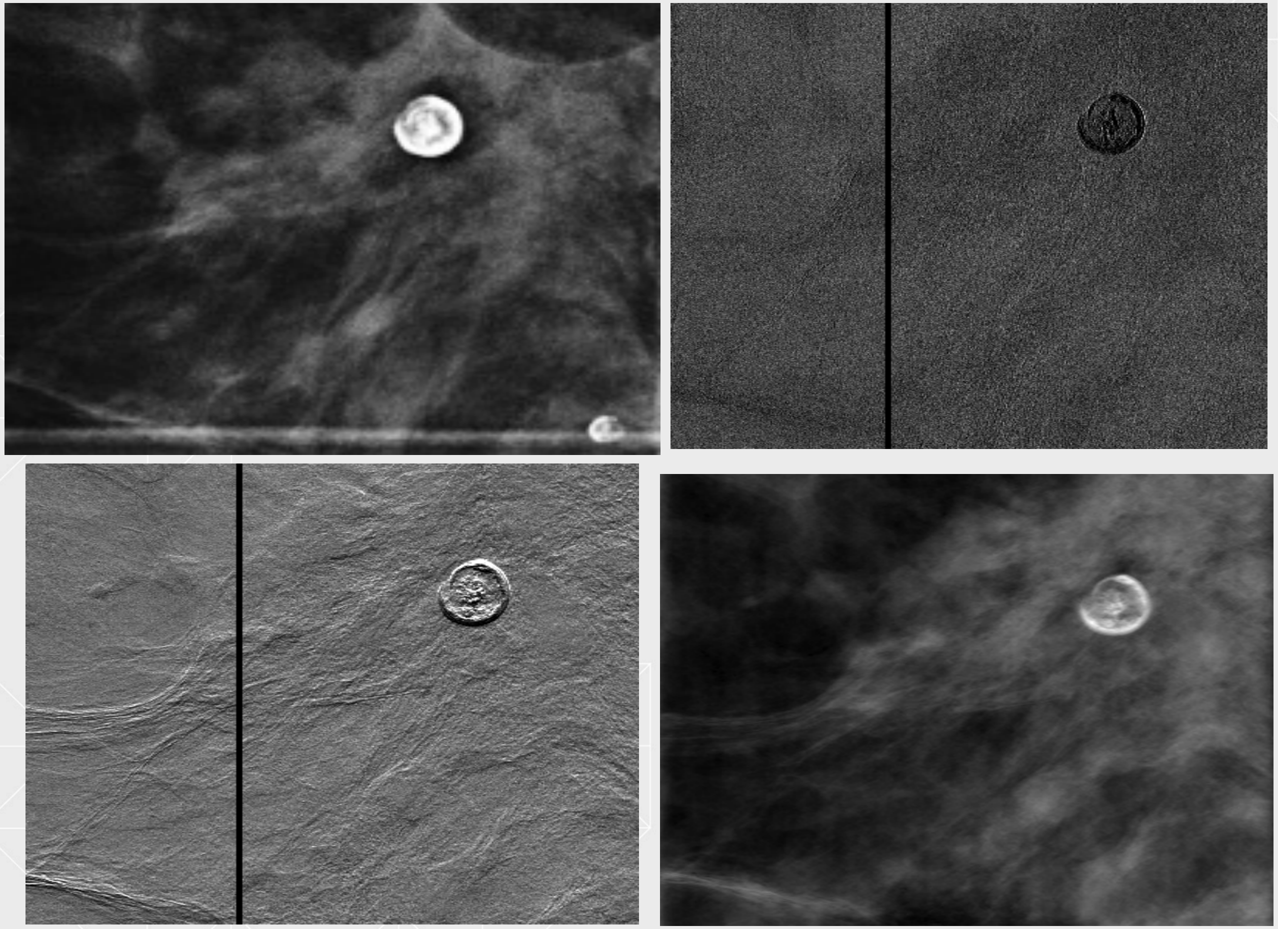
Applications of ultra-high sensitivity/1: detection of tumour invasion at single cell level





Unpublished

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



Total entrance dose = 0.115 mGy

Diemoz et al, Phys. Med. Biol., under review

Conclusions:

X-Ray Phase Contrast Imaging (XPCI) has the potential to transform all applications of x-ray imaging – in medicine and beyond (materials science, security, industrial, cultural heritage etc)

Most XPCI methods work best with coherent sources: high x-ray fluxes generated by small focal spots, ideally placed at a large distance from the imaged object.

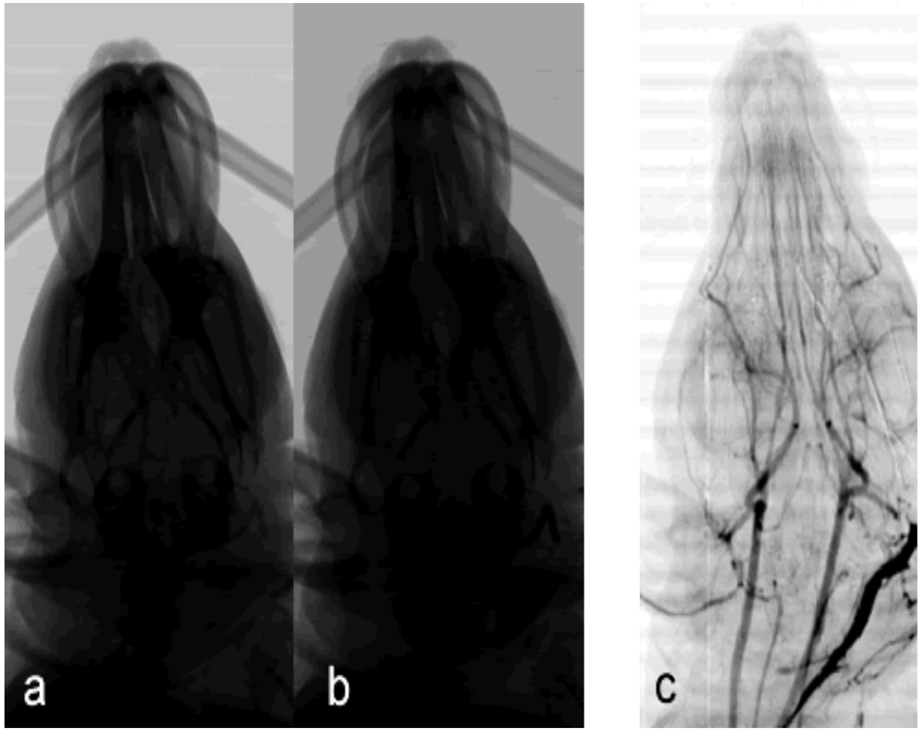
Monochromaticity is also beneficial to many XPCI approaches – this is again linked to flux, as a sufficiently high flux allows for monochromatisation by e.g. perfect crystals

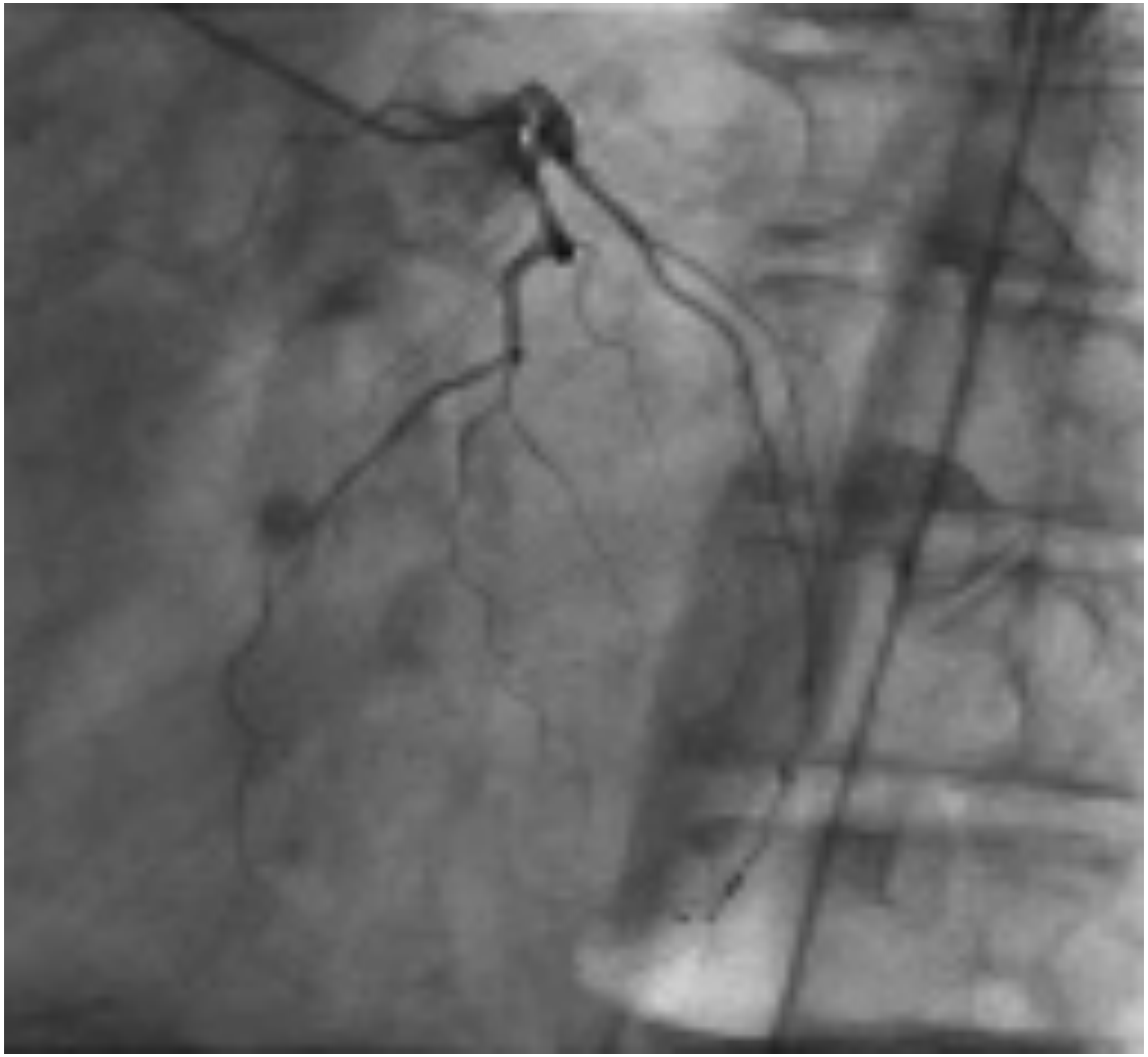
At the moment this effectively means SYNCHROTRONS: >100M, size of a football stadium, ~50 in the world.

Methods start to emerge that allow XPCI to be performed with conventional sources – e.g. "Edge Illumination" (EI) pioneered at UCL

HOWEVER also in that case the availability of coherent sources with fluxes leads to transformative possibilities and opens the way to scientific applications which are currently inaccessible.

Absorption edge of Iodine at 33keV - Both images taken AFTER the contrast agent was injected - but above & below K-edge!



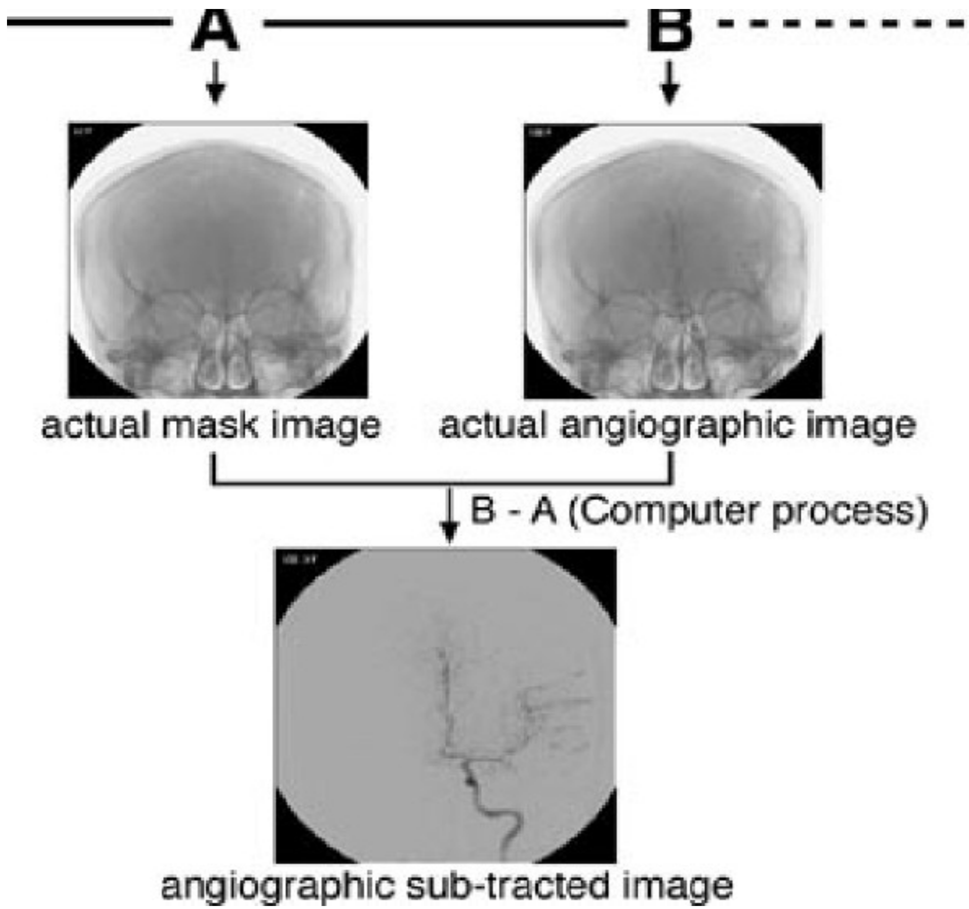


http://faxil.leeds.ac.uk/gallery/interventional/fd20/

http://faxil.leeds.ac.uk/gallery/neuro/

Digital Subtraction Angiography (DSA)

- Take image before and after **contrast agent** delivered
- Subtract images
- Image of contrast agent alone



Sometimes done in FLUOROSCOPY mode: you see the contrast agent as it diffuses!

Source requirements

The minimum energy for medical imaging is ~20 keV. It would be good to be able to go up to 100 keV. For many application spectral width is not an issue - 10-20% more than sufficient; if you want k-edge subtraction too than it becomes critical - e.g. 0.1%.

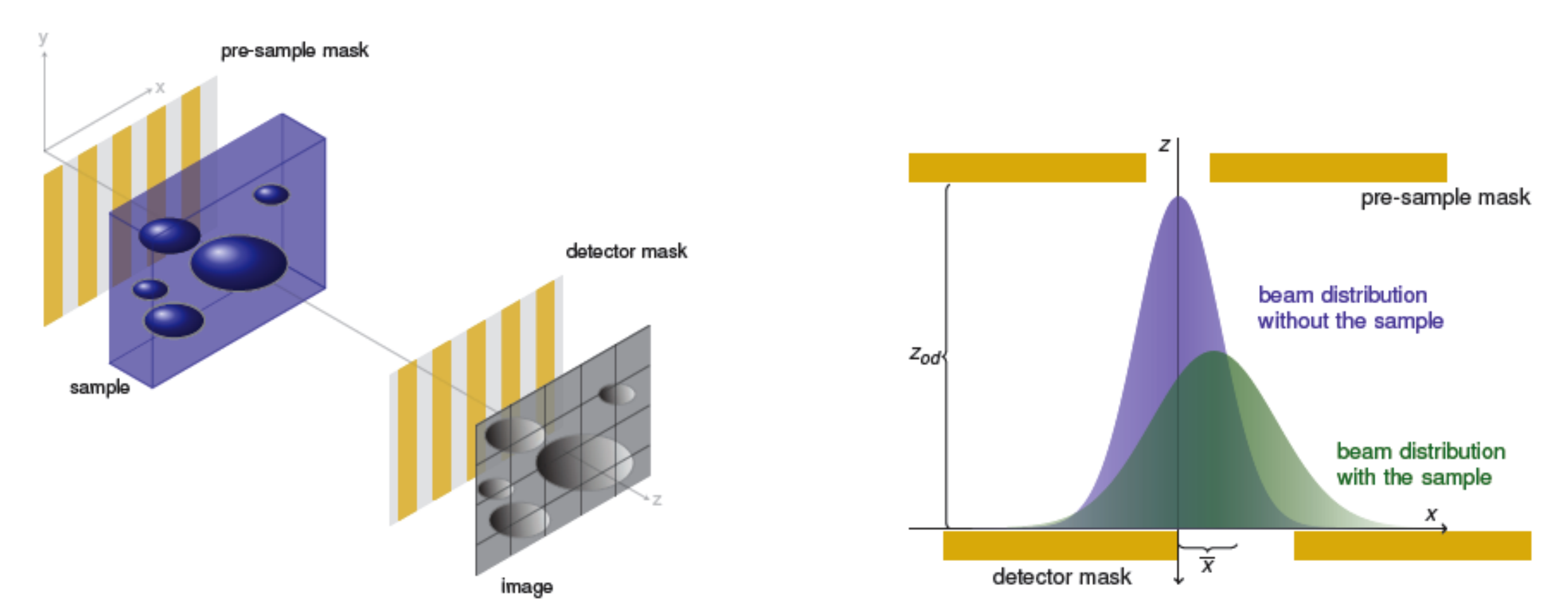
Field of view - depends on application. Mammo is 18 x 24 cm2, everything else larger - ideally up to 40 x 30 cm2. Of course one could start with pre-clinical (e.g. small animal) for which say 12 x 12 cm2 could be sufficient. This drives the divergence question - the smaller, the further away you need to go, i.e. the larger the footprint and (possibly) the cost of the beam transportation system. On top of this there are of course the flux constraints (see below).

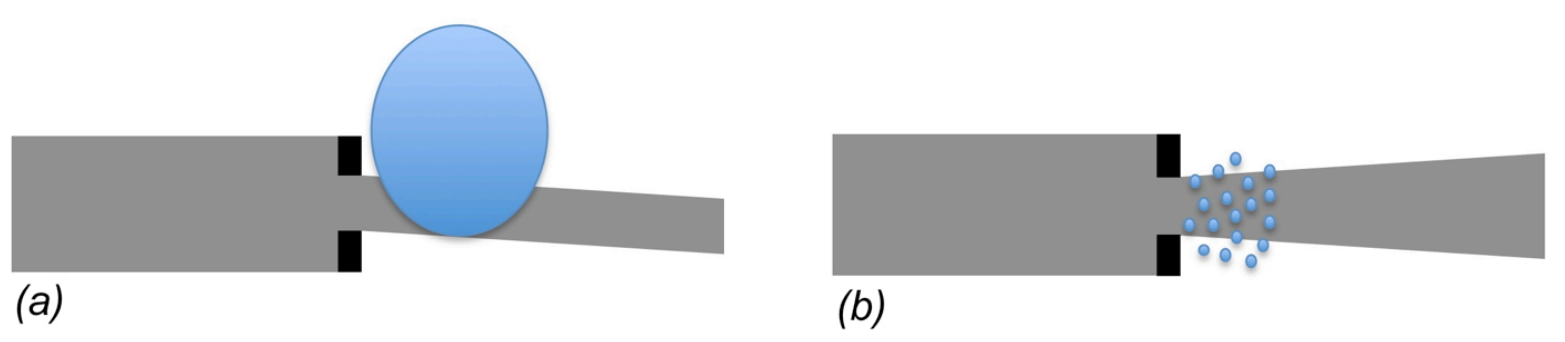
Time structure: we tend to use continuous sources so the answer to that is if you have a repetition rate such that the illumination looks like it's continuous than that's best! In terms of repetition per hour - eventually you might want to do a scan every 10-15 minutes for clinical use; for research purposes including clinical trials it could be lower.

That said in mammo pulsed sources are used, but there should be a lot of x-rays. OFF THE TOP OF MY HEAD I think at Elettra we used ~ 200,000 x-rays per square mm BEHIND the organ which can absorb up to 90%, hence a few million photons per square mm are needed (Alberto please check!)

This could be achieved either in a single pulse, or a series of pulses separated by very short time - such that the total exposure does not exceed say 0.5-1 s.

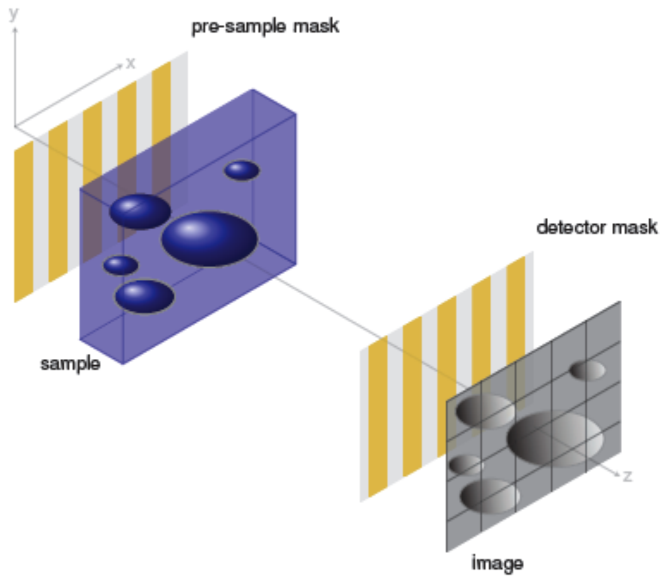
Three-shot DARK FIELD IMAGING retrieval

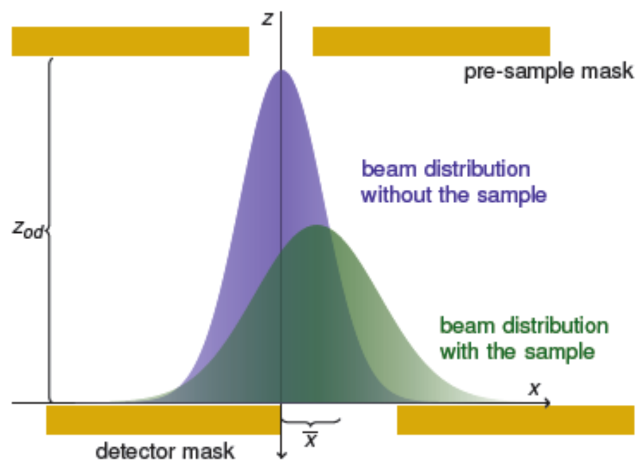


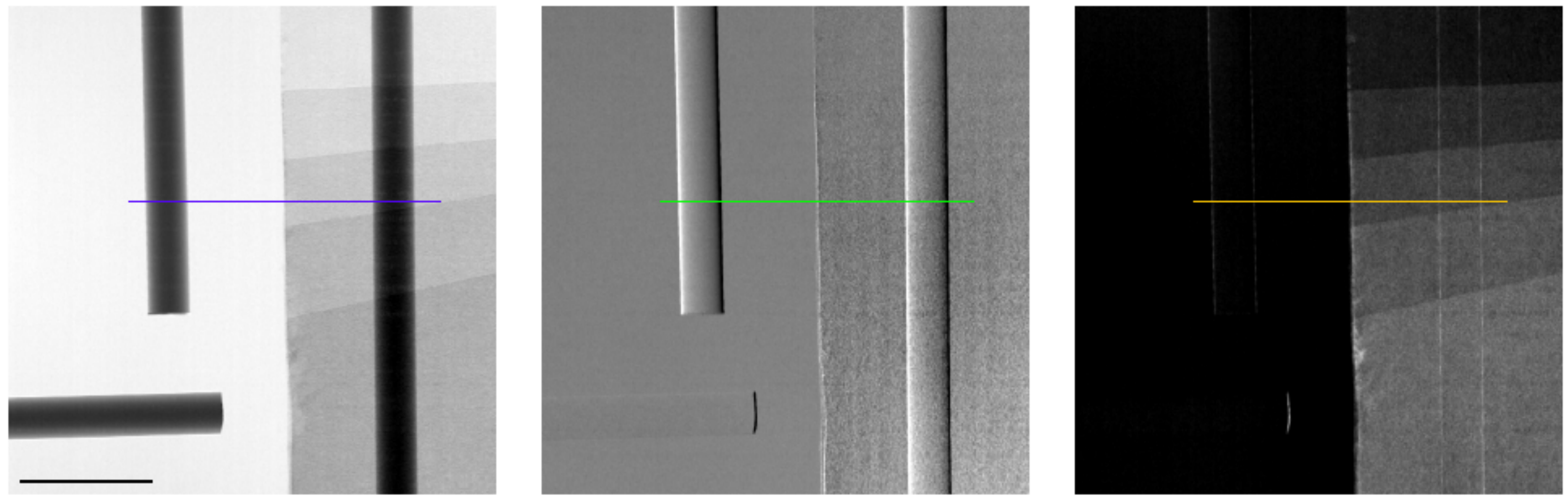


Endrizzi *et al*, Appl. Phys. Lett. 104 (2014) 024106

Three-shot DARK FIELD IMAGING retrieval

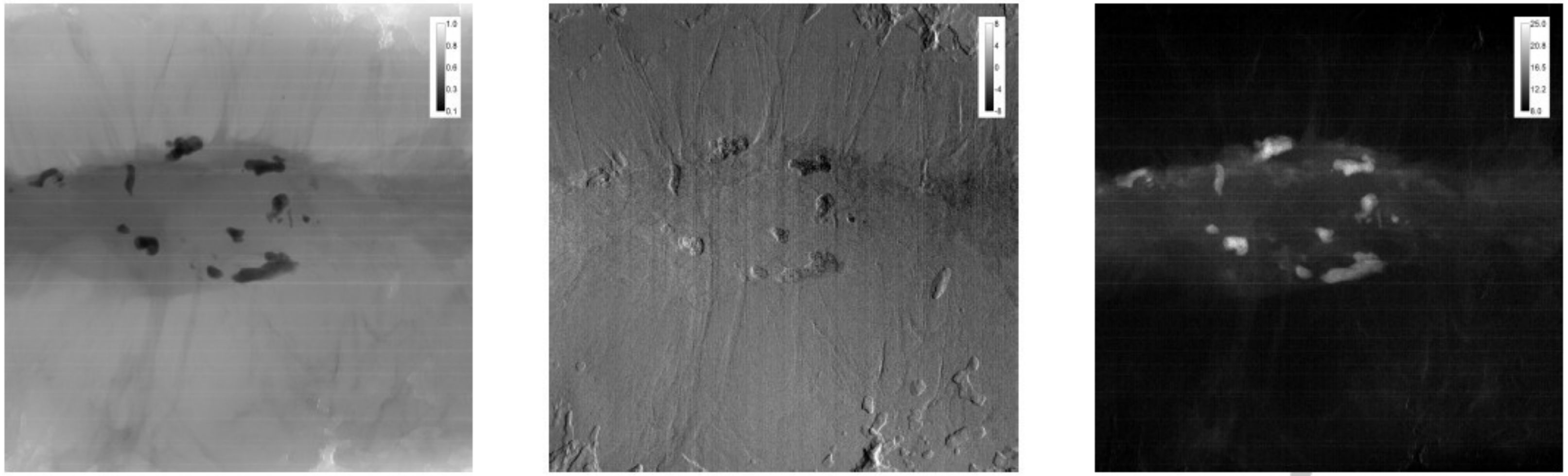






Endrizzi *et al*, Appl. Phys. Lett. 104 (2014) 024106

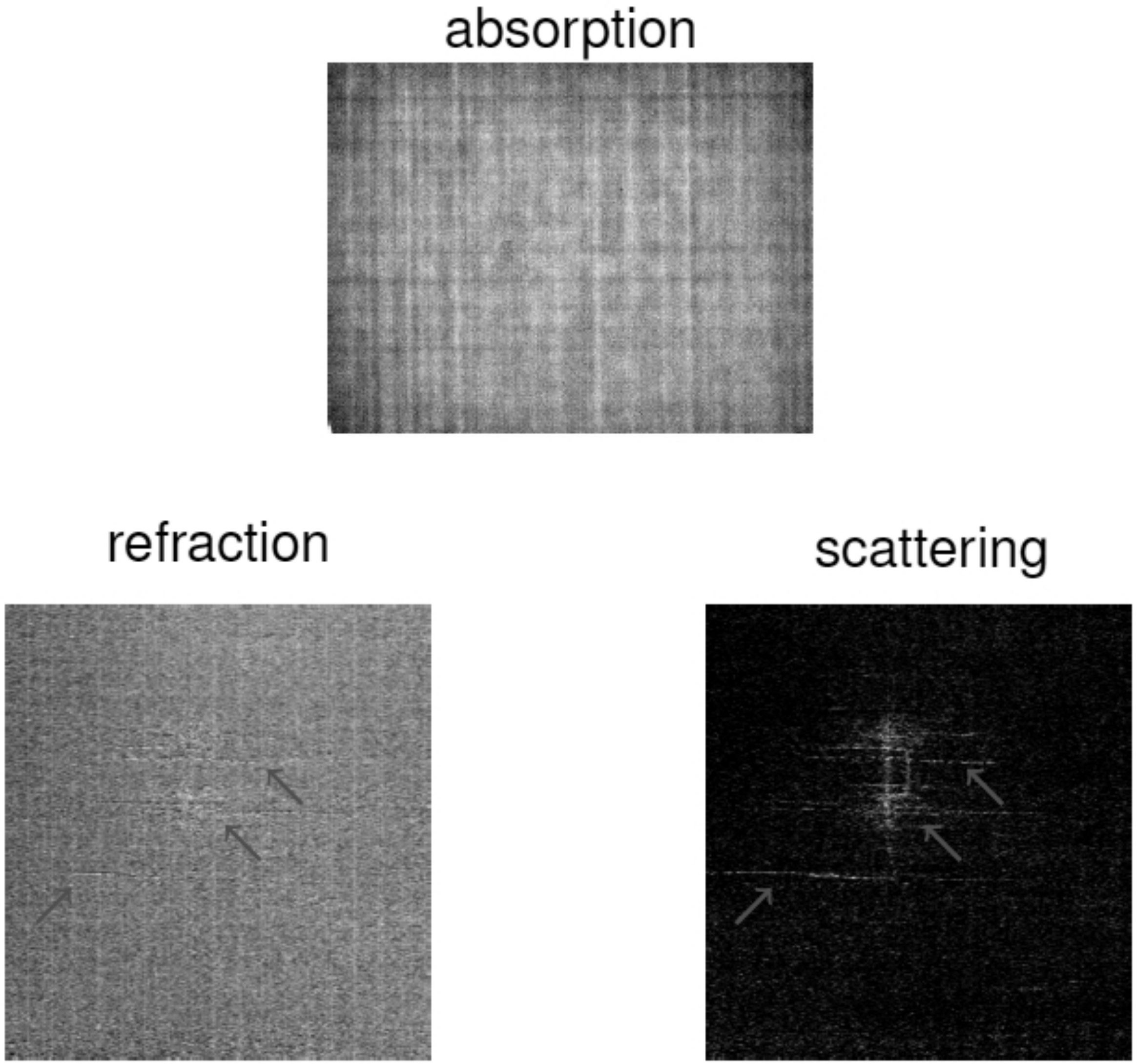
DARK FIELD IMAGING of breast calcifications
3 images only, still within clinical dose limits!



(a) transmission (relative intensity) (b) refraction (μrad) (c) scatter (μrad)

ENTRANCE dose 12 mGy (still compatible with mammo)

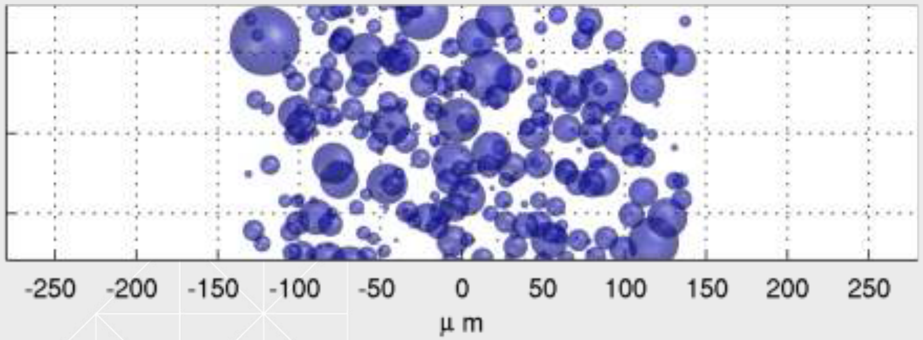
Endrizzi *et al*, Appl. Phys. Lett. 104 (2014) 024106

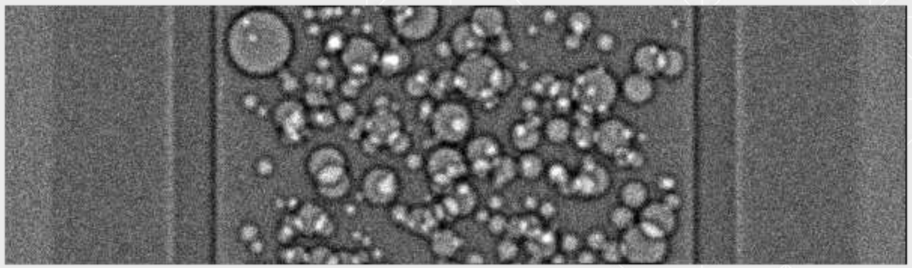


Non-medical applications: testing of composite materials

Endrizzi *et al*, Compos. Struct. 134 (2015) 895-9

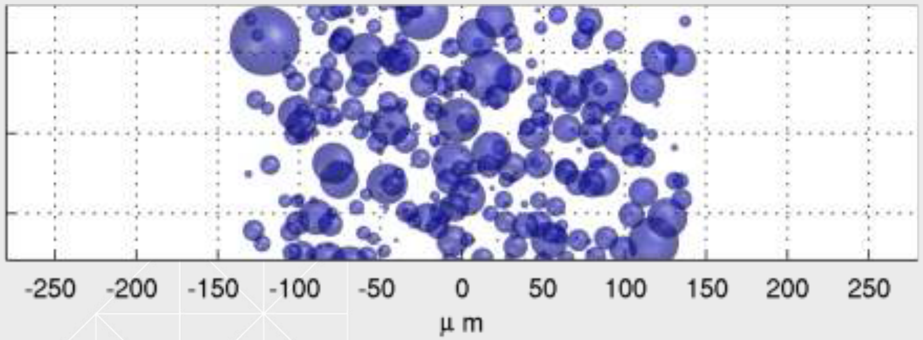
Microbubbles:
a new concept of "phase-based" x-ray contrast agent

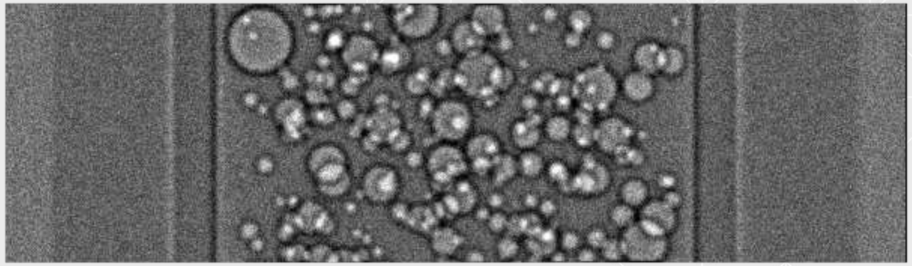




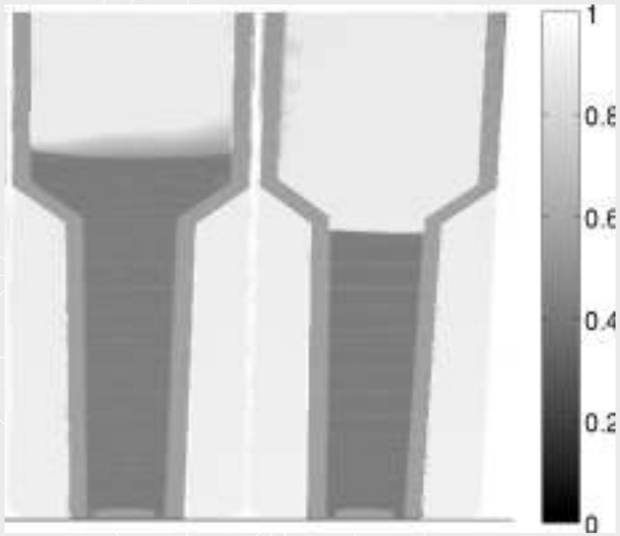
Millard et al. Appl. Phys. Lett. 103 (2013) 114105

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



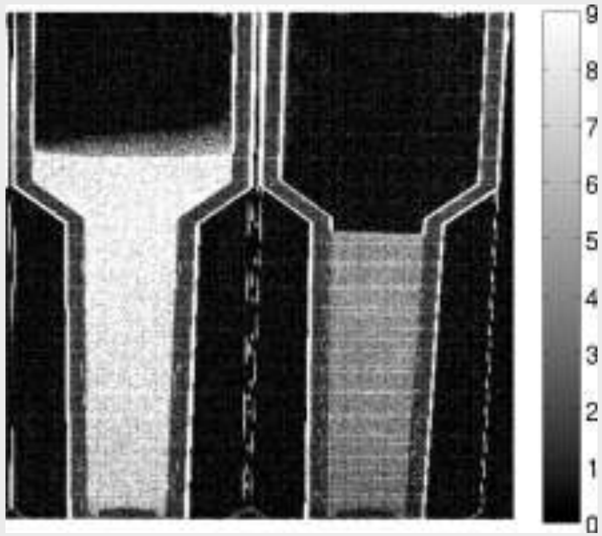


absorption



bubbles no bubbles

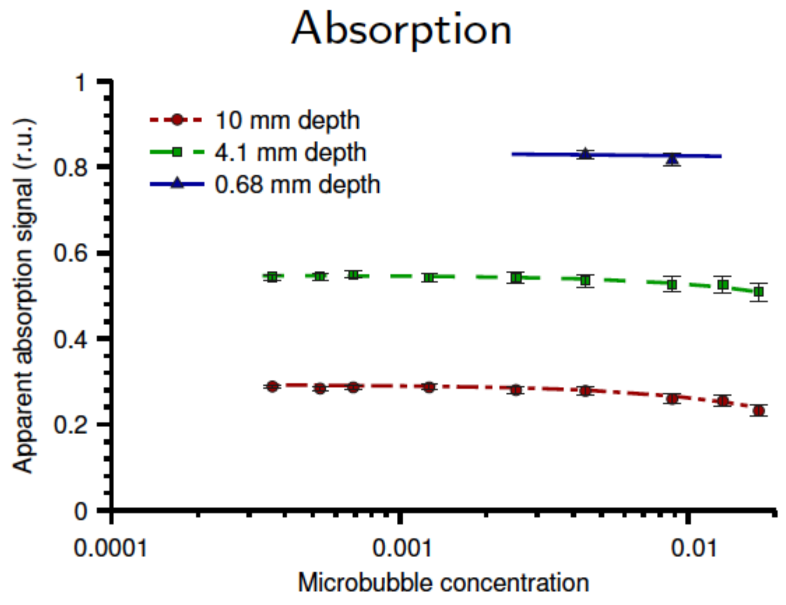
dark field

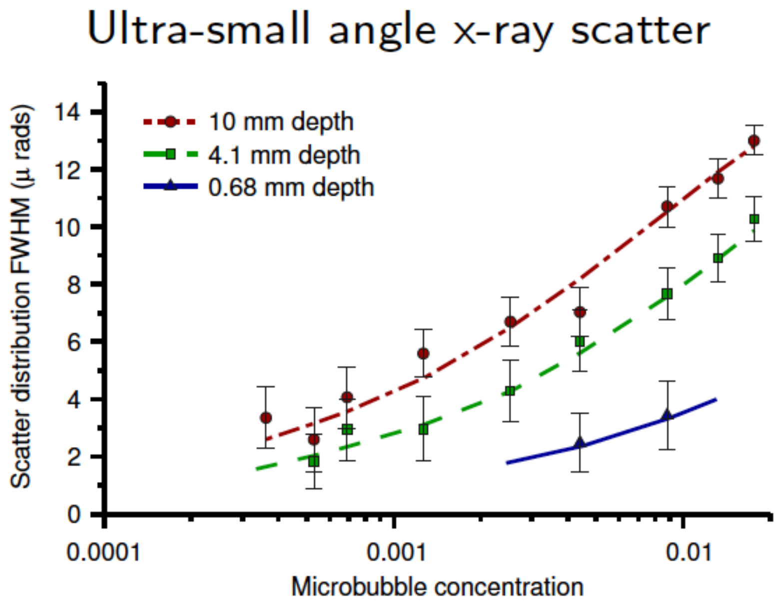


bubbles no bubbles

Millard et al. Appl. Phys. Lett. 103 (2013) 114105

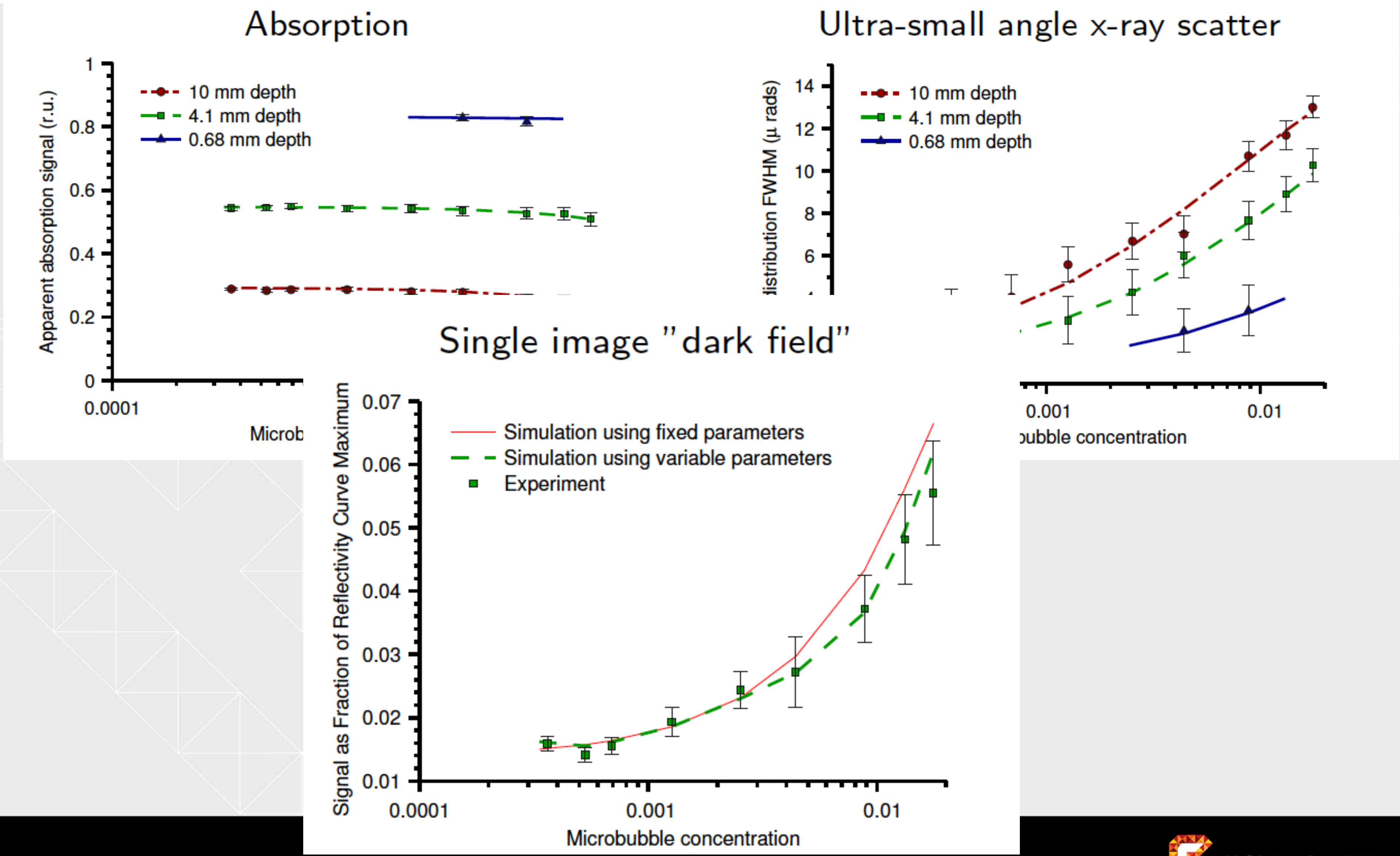
Quantitative extraction of microbubble concentration





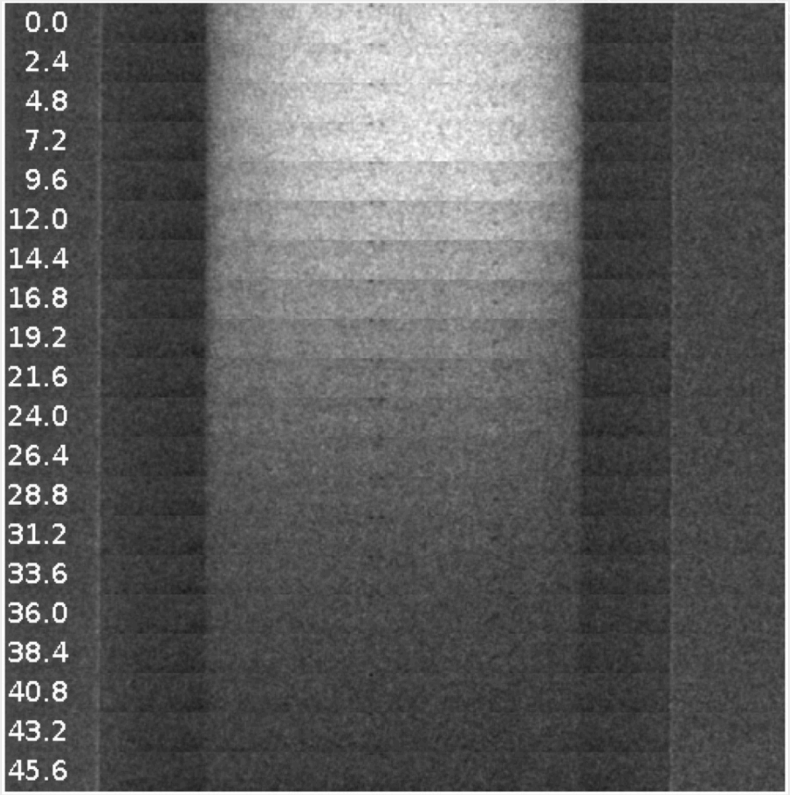
Millard et al. Appl. Phys. Lett. 103 (2013) 114105

Quantitative extraction of microbubble concentration



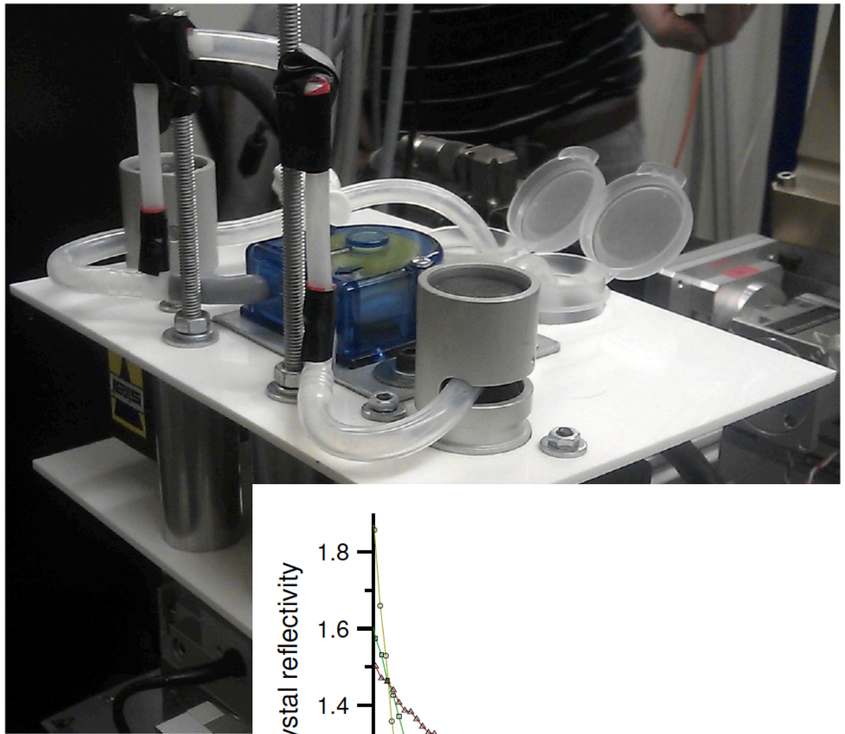
Millard et al. Appl. Phys. Lett. 103 (2013) 114105

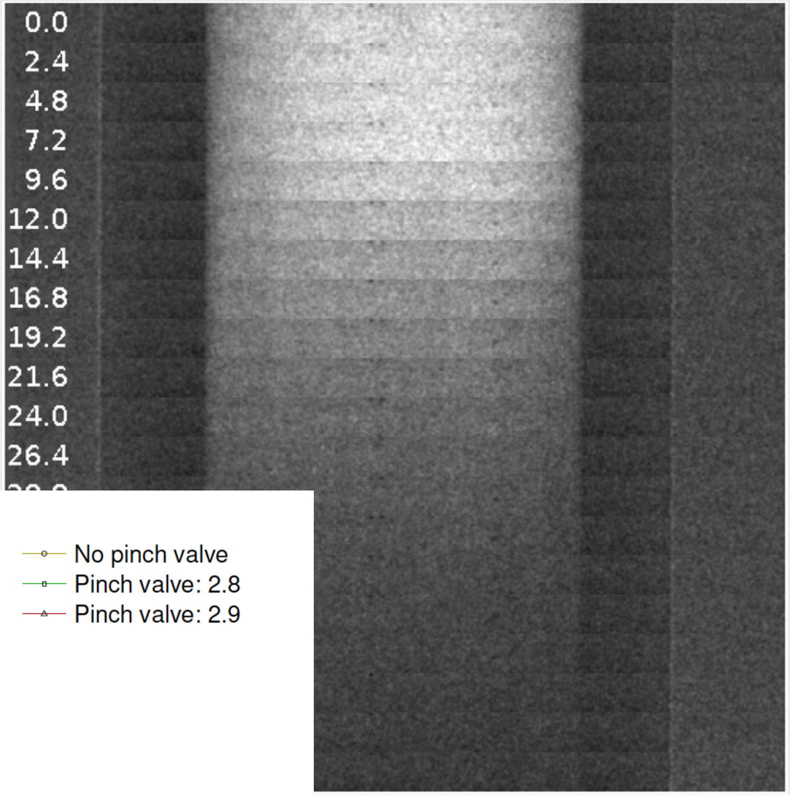
DYNAMIC
quantitative extraction of microbubble concentration

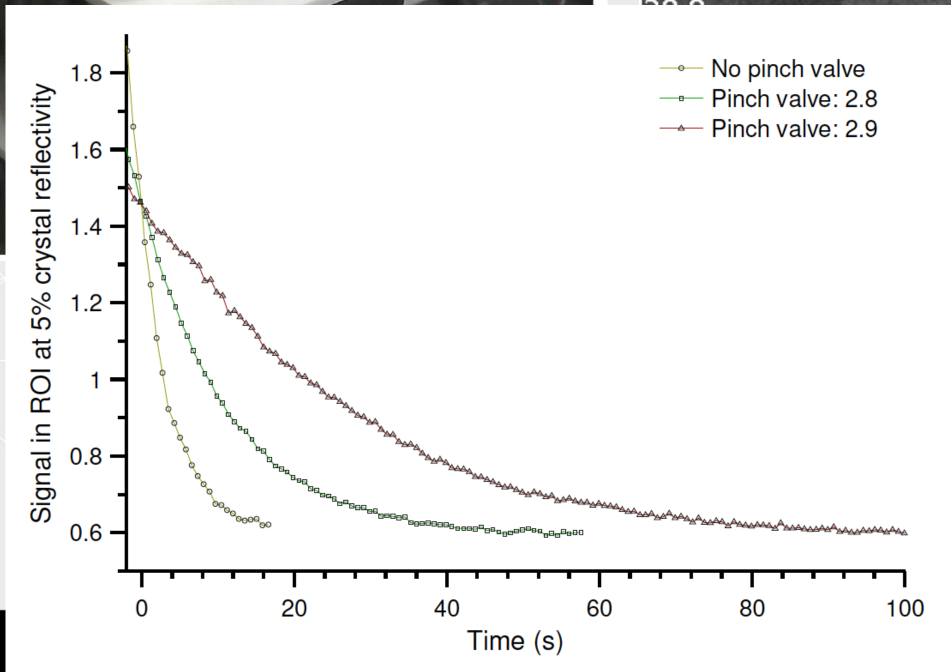


Millard et al., Sci. Rep. 5 (2015) 12509

DYNAMIC
quantitative extraction of microbubble concentration

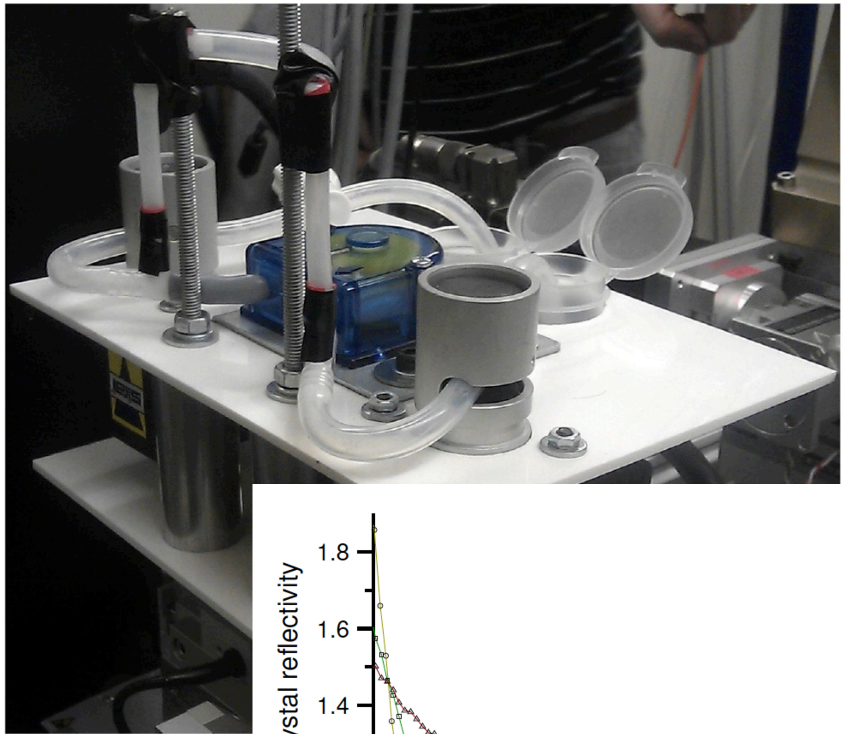


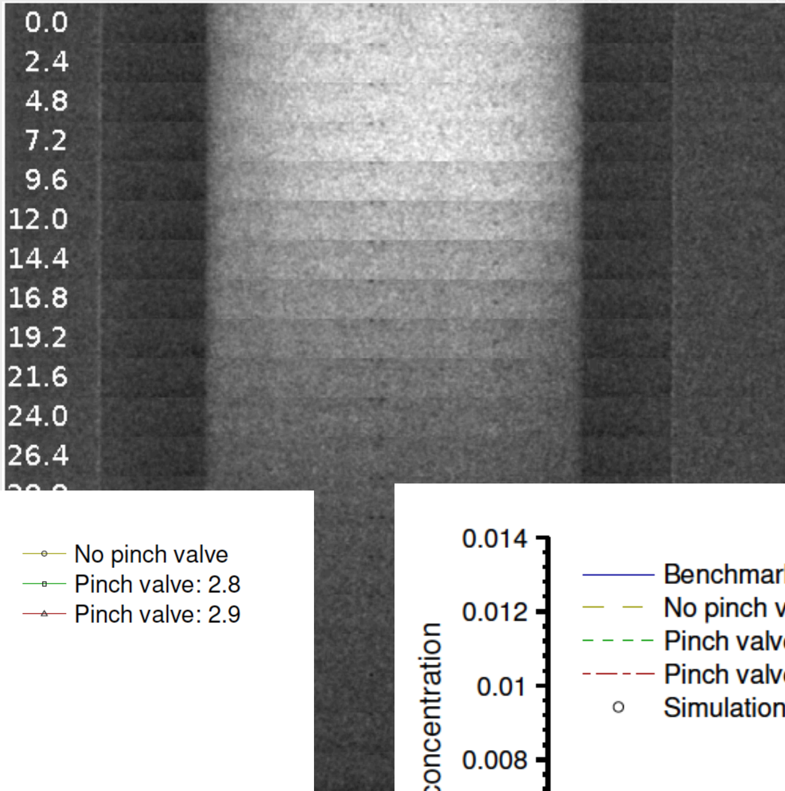


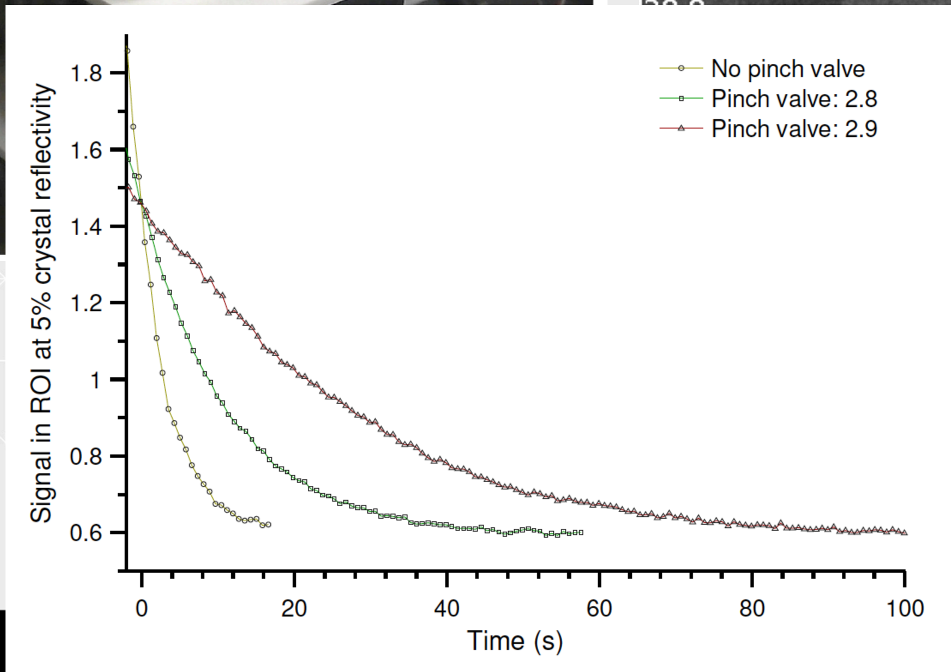


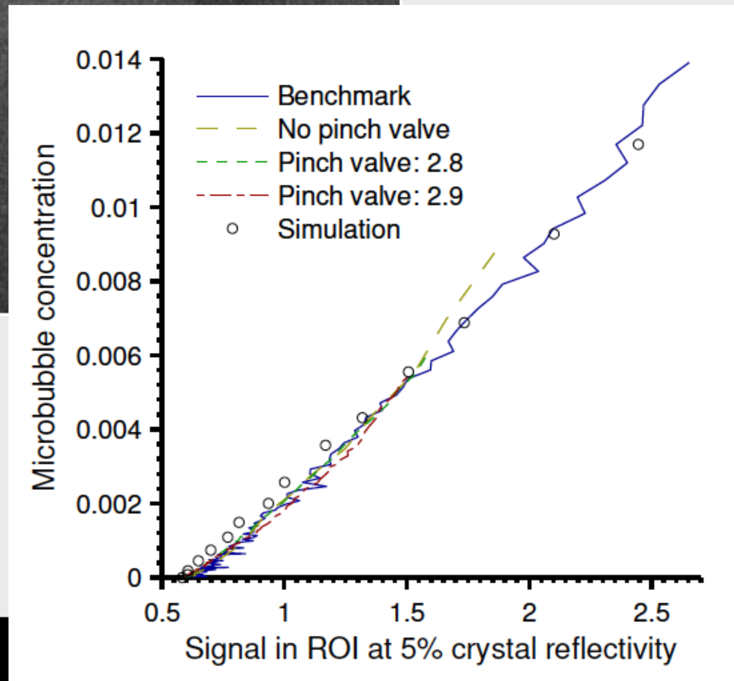
Millard et al., Sci. Rep. 5 (2015) 12509

DYNAMIC
quantitative extraction of microbubble concentration





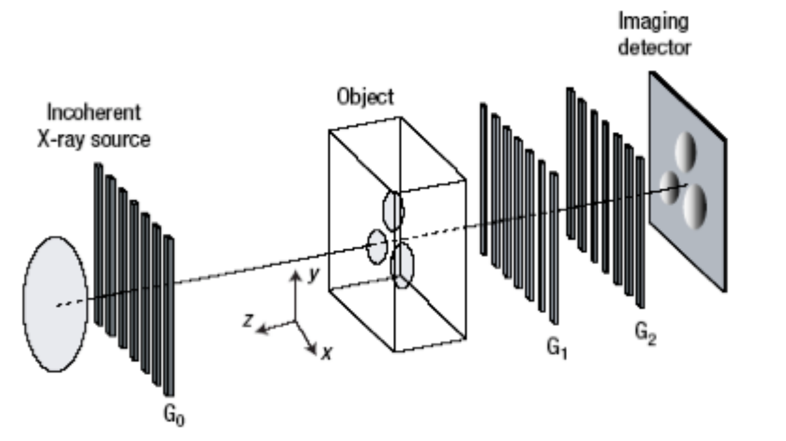


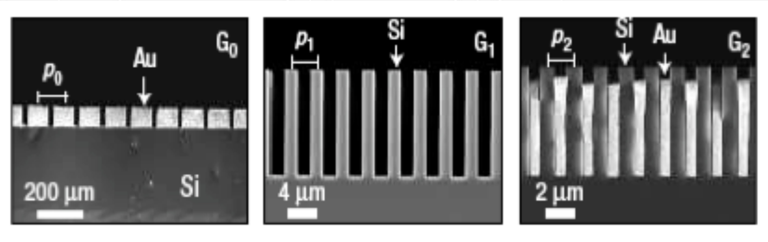


Millard et al., Sci. Rep. 5 (2015) 12509

Interlude: **the TALBOT/LAU interferometer (a.k.a. different methods/3):**

much smaller pitches, and based on a coherent effect

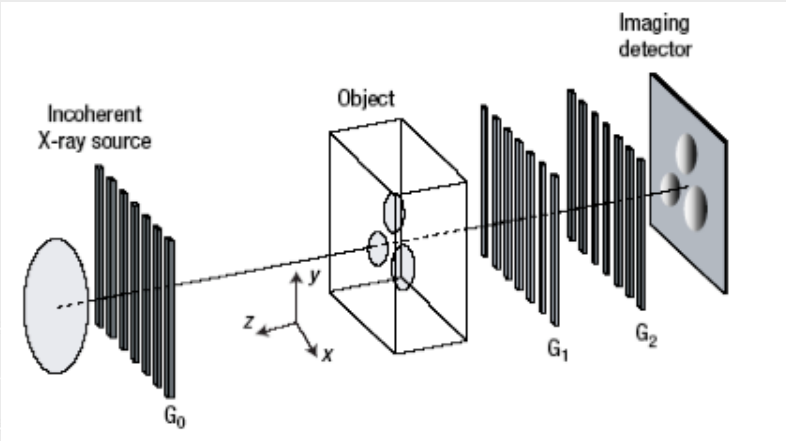


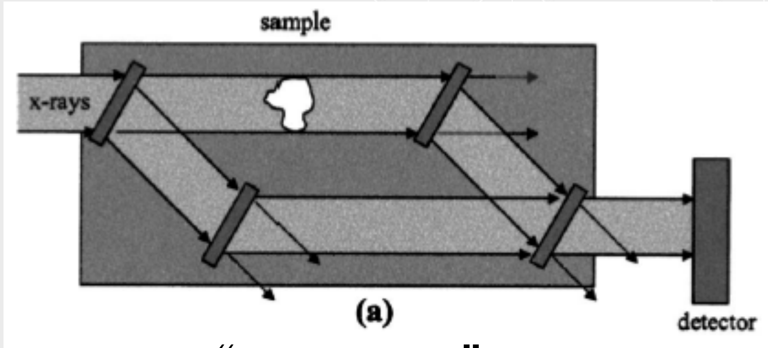


The used gratings, obtained through microfabrication techniques

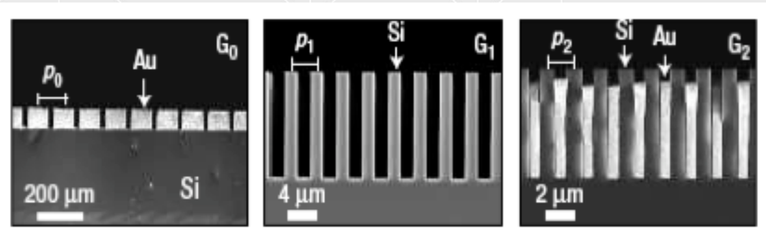
Synchrotron: David et al APL 81 (2002) 3287-9, Momose et al Jpn J Appl Phys 42 (2003) L866-8; Lab source Pfeiffer *et al*, Nature Physics **2** (2006) 258-61

Interlude: **the TALBOT/LAU interferometer (a.k.a. different methods/3):** much smaller pitches, and based on a coherent effect





The classic, "Bonse-Hart" interferometer



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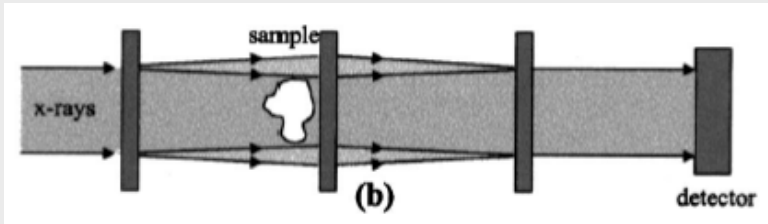
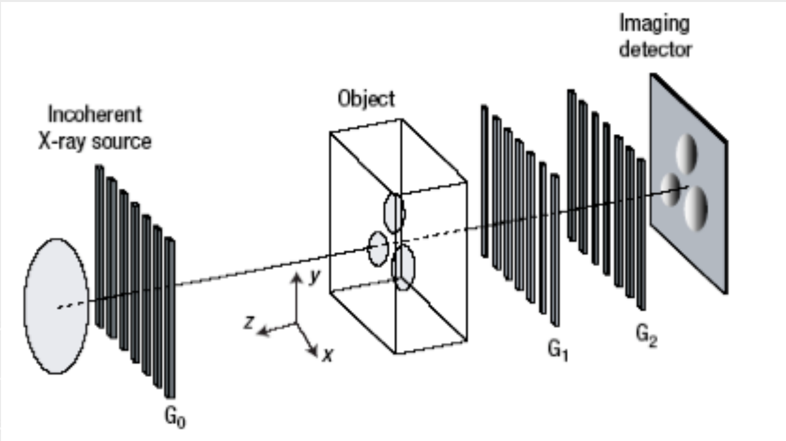
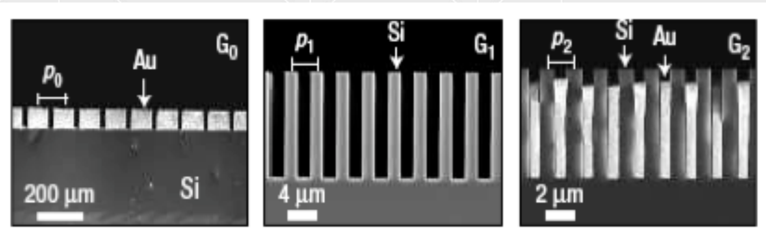


The shearing interferometer

Synchrotron: David et al APL 81 (2002) 3287-9, Momose et al Jpn J Appl Phys 42 (2003) L866-8; Lab source Pfeiffer *et al*, Nature Physics **2** (2006) 258-61

Interlude: **the TALBOT/LAU interferometer (a.k.a. different methods/3):** much smaller pitches, and based on a coherent effect





The used gratings, obtained through microfabrication techniques

- 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 (pitches 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)

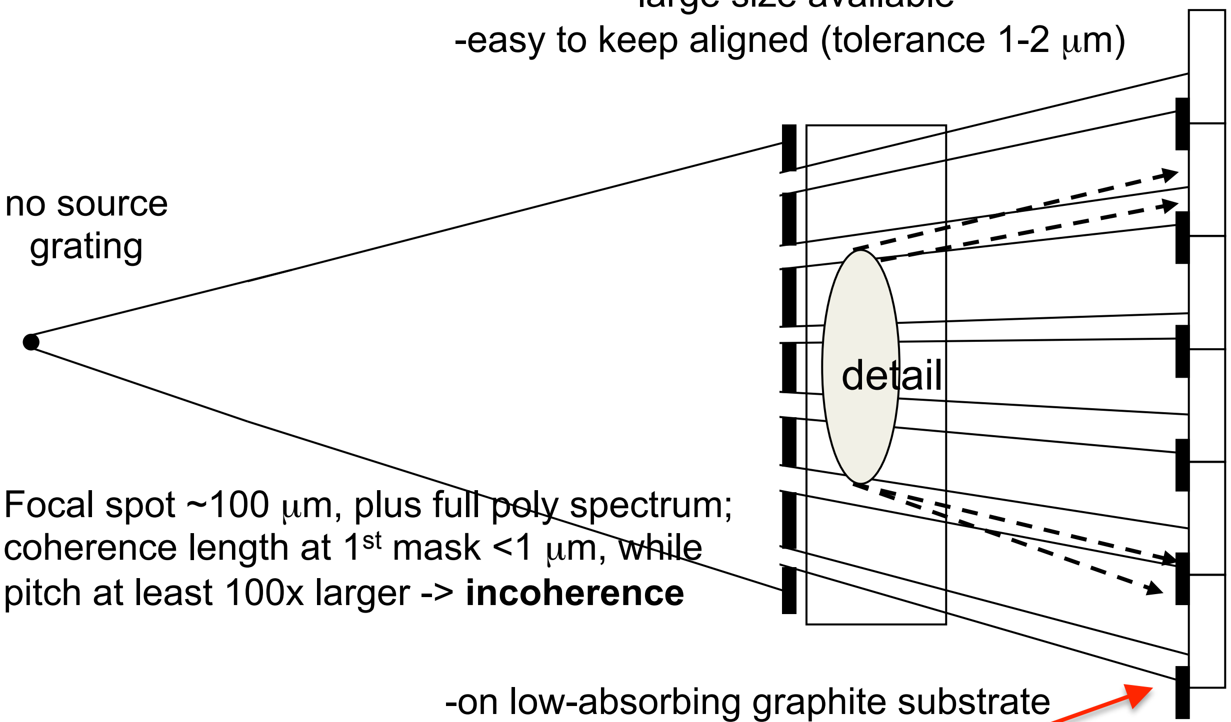
- the field of view is currently limited to ~6x6 cm^2

Synchrotron: David et al APL 81 (2002) 3287-9, Momose et al Jpn J Appl Phys 42 (2003) L866-8; Lab source Pfeiffer *et al*, Nature Physics **2** (2006) 258-61

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)

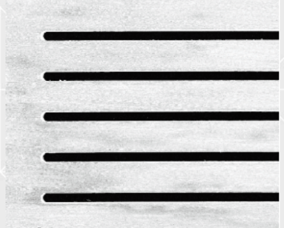
no source grating



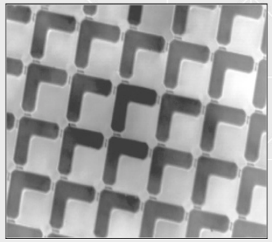
Focal spot ~100 μm, plus full poly spectrum; coherence length at 1st mask <1 μm, while pitch at least 100x larger -> **incoherence**

-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:

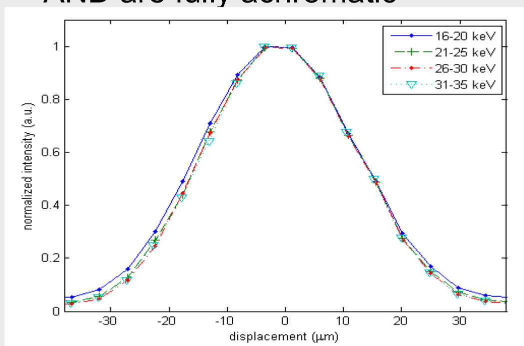


OR:



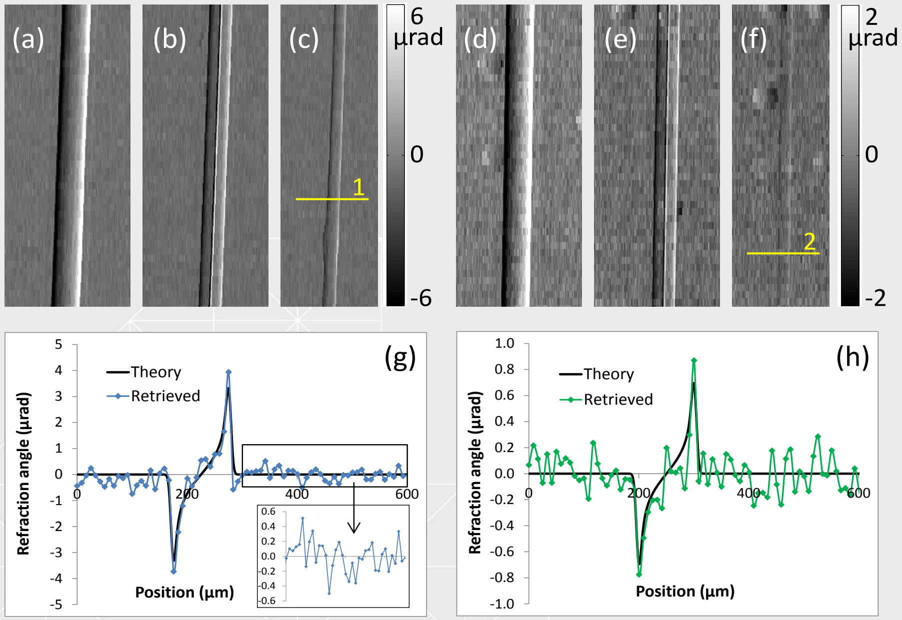
For 2D sensitivity (see Olivo *et al* APL **94** (2009) 044108)

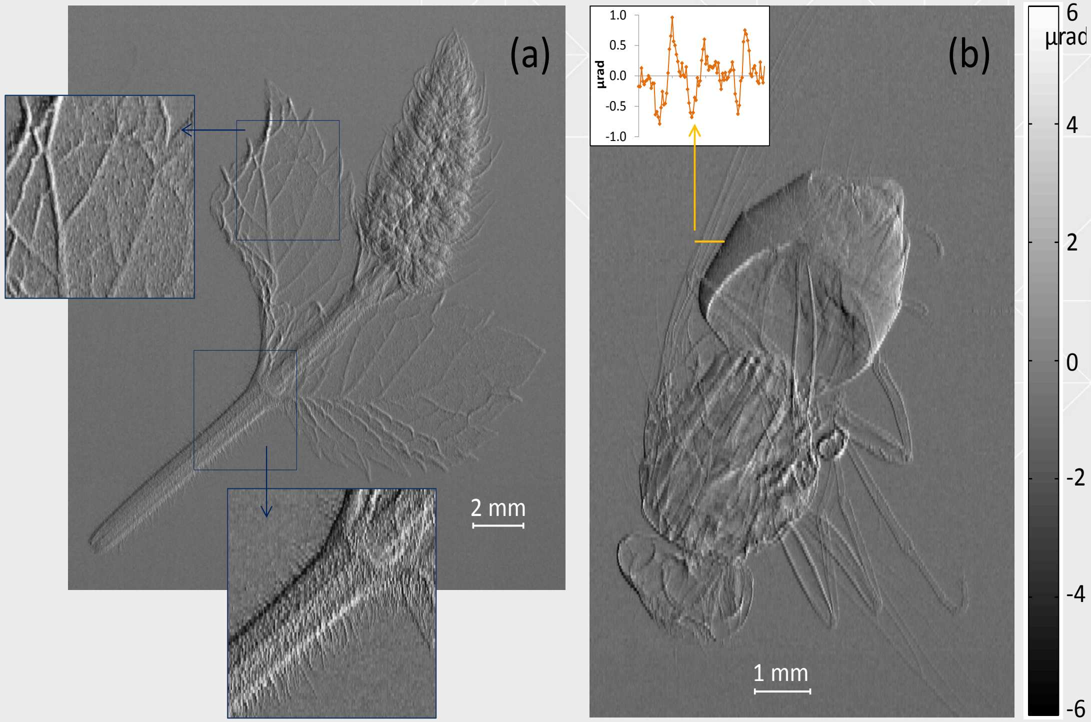
AND are fully achromatic



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

More on the sensitivity of the lab system:



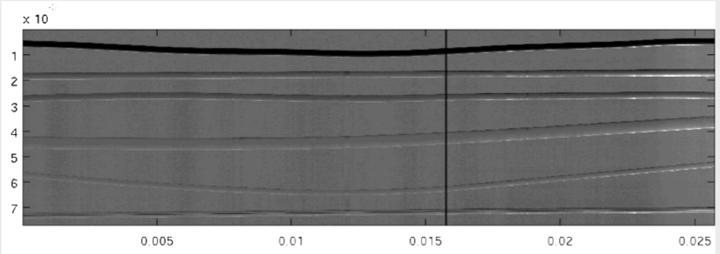


$$\Delta\theta_{x,eff} = \frac{1}{z_{od}} R^{-1}\left(\frac{I_{obj,+}}{I_{obj,-}}\right) \longrightarrow \sigma\left(\Delta\theta_{x,eff}\right); \quad \frac{\sqrt{C\left(x_{e,+}\right)}}{z_{od}\sqrt{2TI_0}\left[\rho_{ref,n}\left(x_{e,+}\right)-\rho_{ref,n}\left(x_{e,+}+d\right)\right]}$$

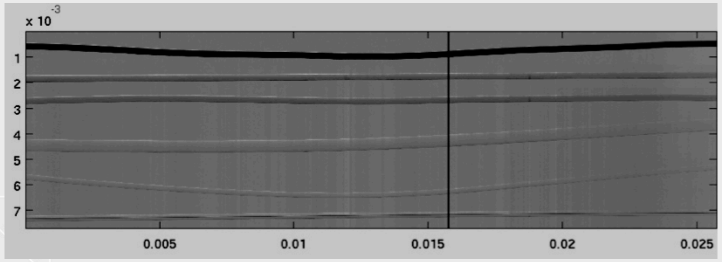
This gives a phase sensitivity of ~ 270 nRad, with only 2 images x 7s exposure each; same as reported by Thuring (Stampanoni's group) for GI. Revol reported a sensitivity of about 110 nRad but with 12 x 7s frames – as one can expect the value to scale with sqrt(exp time), that also fits.

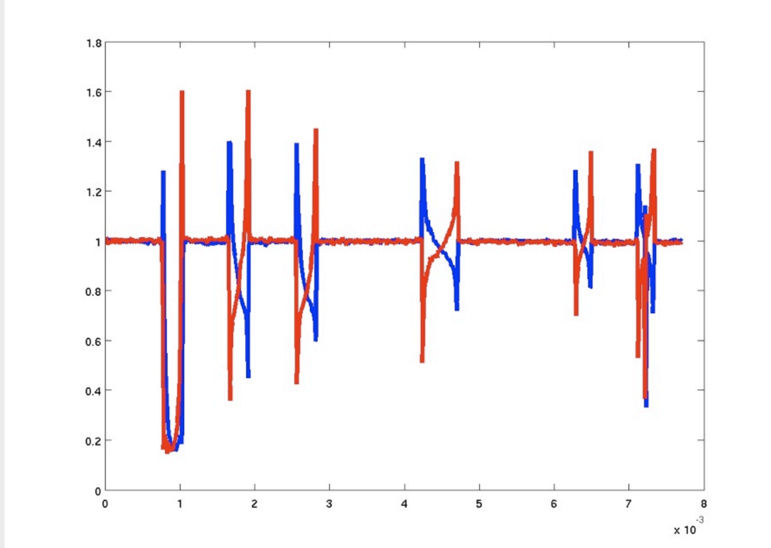
Quantitative phase contrast imaging

"SLOPE -"

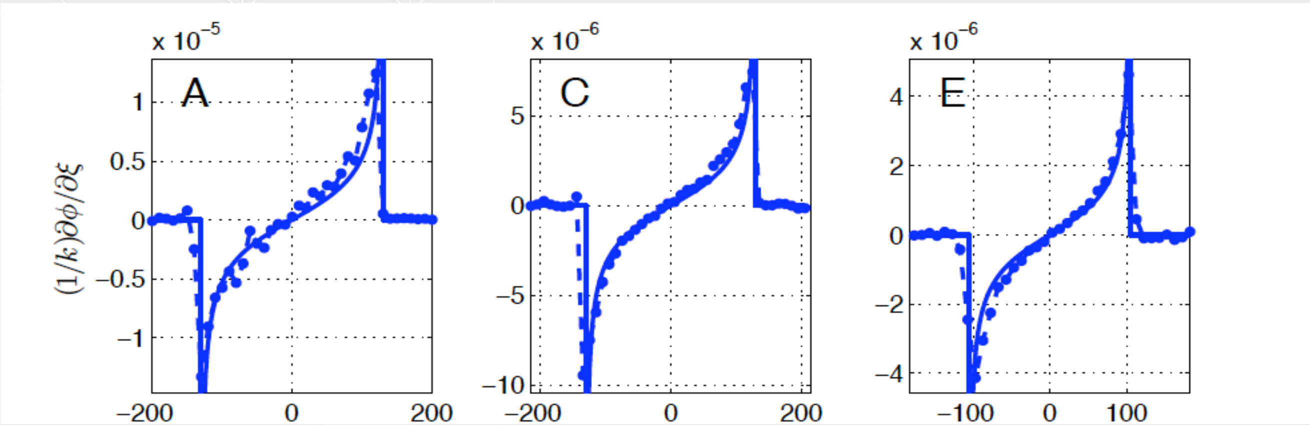


"SLOPE +"





Titanium Aluminum PEEK



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

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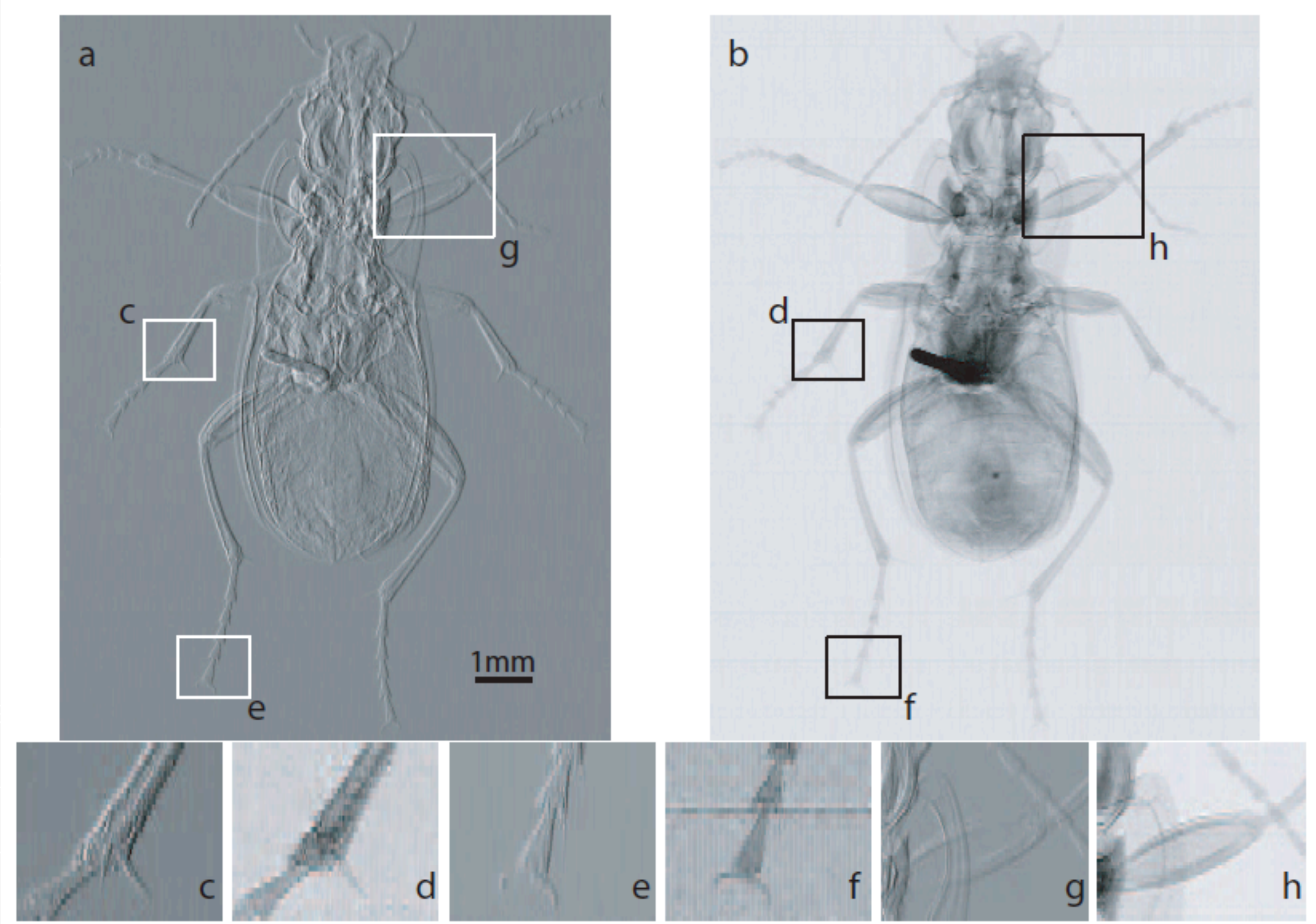
Munro *et al* Opt. Exp. 21 (2013) 647-61

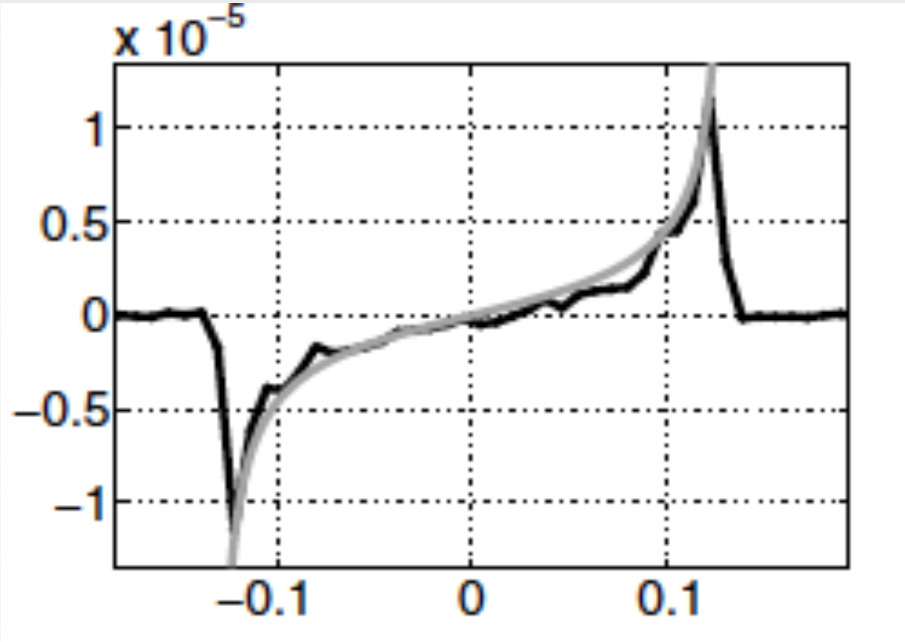
Quantitative phase contrast imaging



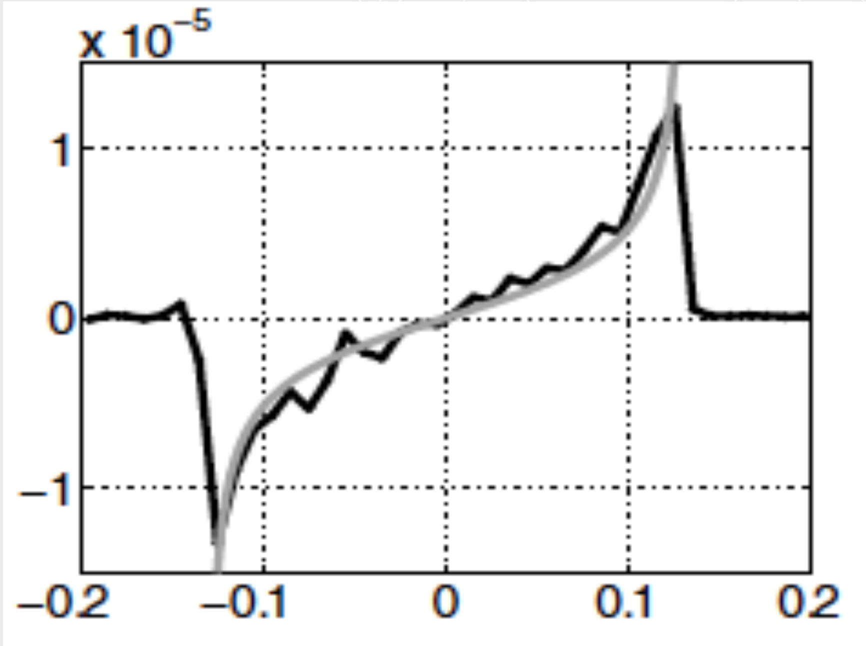
P. Munro *et al*, *PNAS* 109 (2012) 13922-7

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)

Munro *et al*, *PNAS* 109 (2012) 13922-7