Phase contrast medical imaging with compact X-ray sources: towards clinical applications

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ESRF

ID17 Biomedical Beamline
European Synchrotron Radiation Facility

Porto Conte – September 9th, 2008

“Munich-Centre for Advanced Photonics” *MAP* project

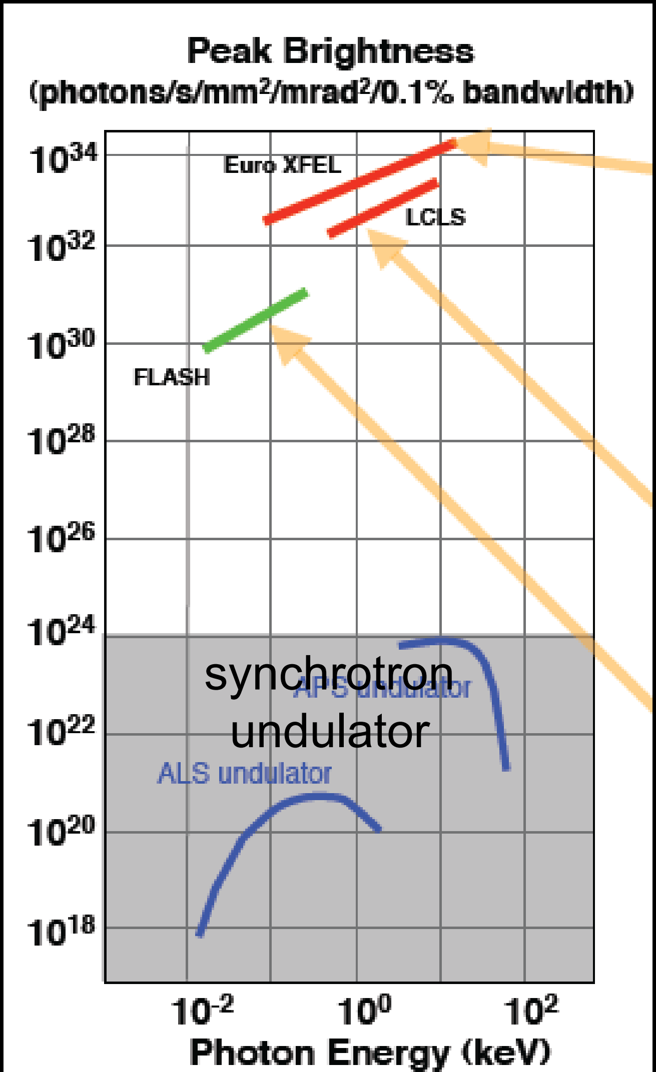
MAP aim and structure

MAP X-ray source design

Role of the ESRF: biomedical applications

"Munich-Centre for Advanced Photonics"
MAP project

Cluster of Excellence of the German Research Foundation (DFG) financed with 42 M€



MAIN AIM:

compact source of

brilliant high-flux X-ray beams,

high X-ray energies (e.g. 60 keV)

Installation of this X-ray source
at a University or/and hospital
is the ultimate goal

MAP research areas

A PHOTON AND PARTICLE BEAMS

A.1 | Next-generation light sources

A.2 | Brilliant particle and photon sources

B FUNDAMENTAL INTERACTIONS AND QUANTUM ENGINEERING

B.1 | Fundamental physics and nuclear transitions

B.2 | Optical transitions and quantum engineering

C STRUCTURE AND DYNAMICS OF MATTER

C.1 | Electron dynamics in atoms, molecules, solids and plasmas

C.2 | Molecular dynamics and elementary chemical reactions

C.3 | Biomolecules and nano-assemblies

D ADVANCED PHOTONICS FOR MEDICINE

D.1 | Laser-based photon and particle beams for medicine

http://www.munich-photonics.de/

MAP participant institutes

Universities	LMU Ludwig-Maximilians-Universität München	Ludwig-Maximilians-University (LMU)
	TUM Technische Universität München	Technical University Munich (TMU)
Scientific partner	Universität der Bundeswehr München	University of Bundeswehr, Munich
Non-university research	Max-Planck-Gesellschaft	Max Planck Institute of Quantum Optics
	IPP	Max-Planck-Institute for Plasmaphysics
		Max Planck Institute for Biochemistry
	MPE	Max Planck Institute for Extraterrestrial Physics
	Max-Planck-Gesellschaft	Max-Planck-Institut Halbleiterlabor
Industrial partner	SIEMENS	Siemens

The *MAP* X-ray source

The MAP X-ray source: *designs under development*

1 ■ Table-Top X-FEL (TT-XFEL)

laser-plasma accelerator **+** large-scale X-ray free-electron laser **=** Laser-plasma accelerator-based FEL

2 ■ Dense laser-driven electron sheets as relativistic mirrors

Reflection of a laser beam coherently from a dense 50 MeV electron sheet shaped by laser

1 “driver” laser

1 “propagating” laser

1 thin solid-state electron foil

1 ■ Table-Top X-FEL (TT-XFEL)

Grüner *et al*, Appl.Phys. B86, 2007

Design considerations for table-top, laser-based VUV and X-ray free electron lasers

Applied Physics B
Lasers and Optics

2 ■ Dense laser-driven electron sheets as relativistic mirrors

Habs *et al*, Appl.Phys. B, 2008

Dense Laser-driven Electron Sheets as Relativistic Mirrors for Coherent Production of Brilliant X-Ray and γ -Ray Beams.

D. Habs[1,2], M. Hegelich[4], J. Schreiber[1,2], M. Gross[1], A. Henig[1,2], D. Kiefer[1], D. Jung[1]

Applied Physics B
Lasers and Optics

In press

The *MAP* TT-XFEL - **Grüner *et al.* (APB, 2007)**

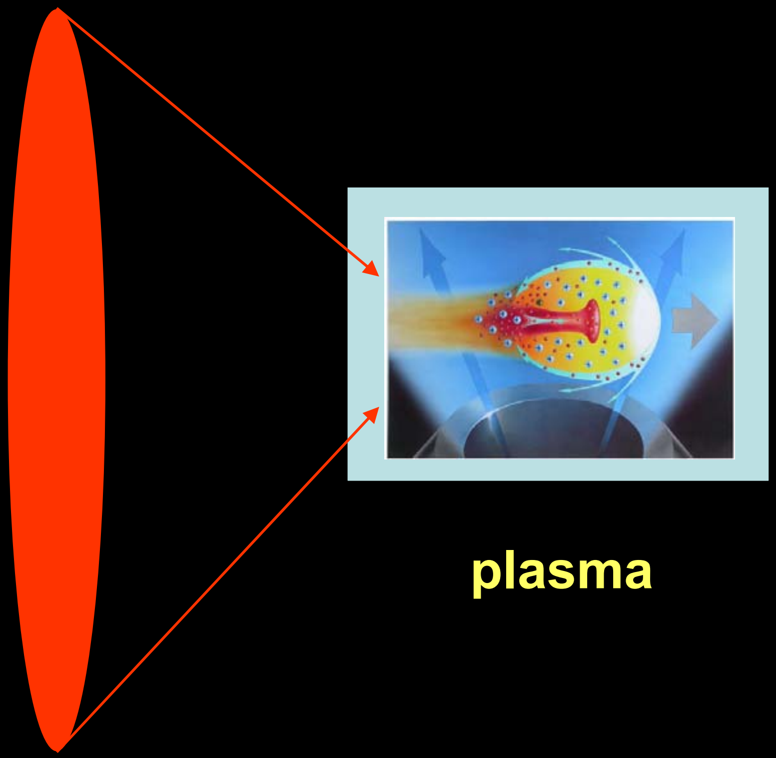
Laser-plasma accelerator

ultra-short, high intensity laser pulse with length shorter than the plasma wavelength (~μm) (corresponding to gas densities of 10^{19} cm^{-3})

High intense (nC charge) quasi monochromatic electron pulse

laser
energy: ~ J
pulse length: ~ 5-50 fs
power: ~ TW to PW

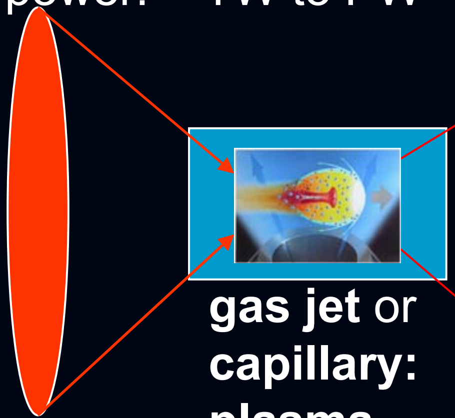
5 fs – Petawatt laser

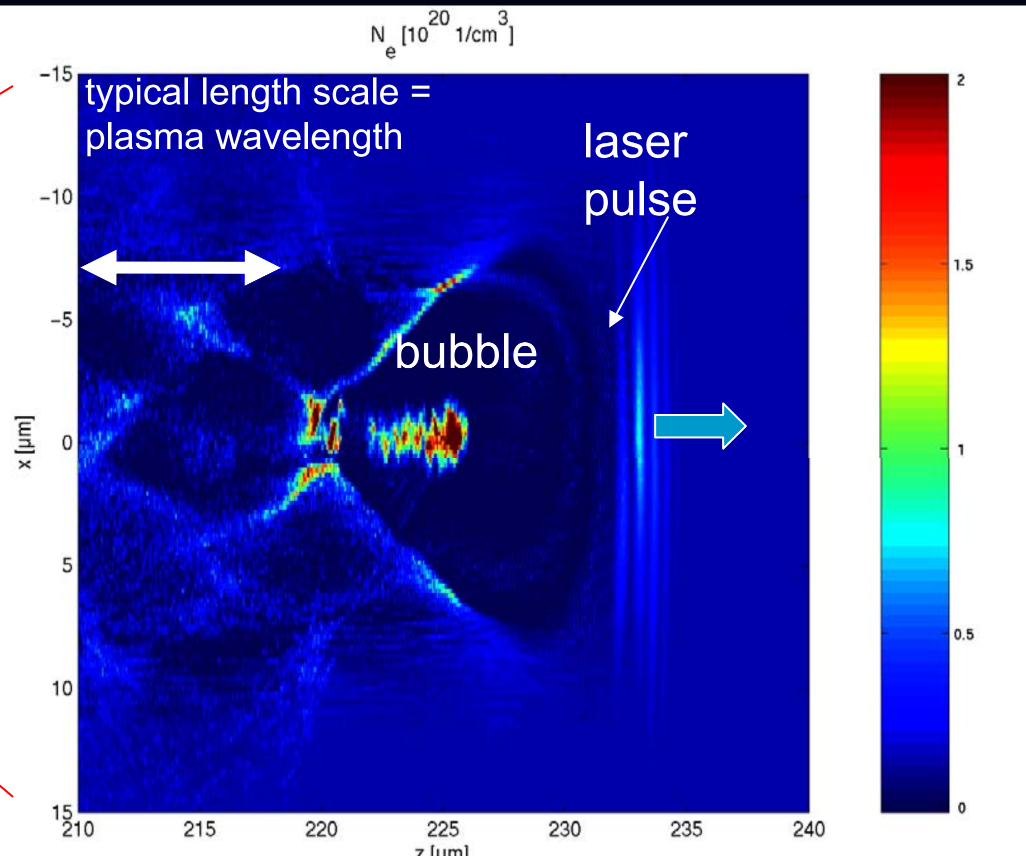


plasma

Laser plasma accelerators

laser
energy: ~ J
pulse length: ~ 5-50 fs
power: ~ TW to PW



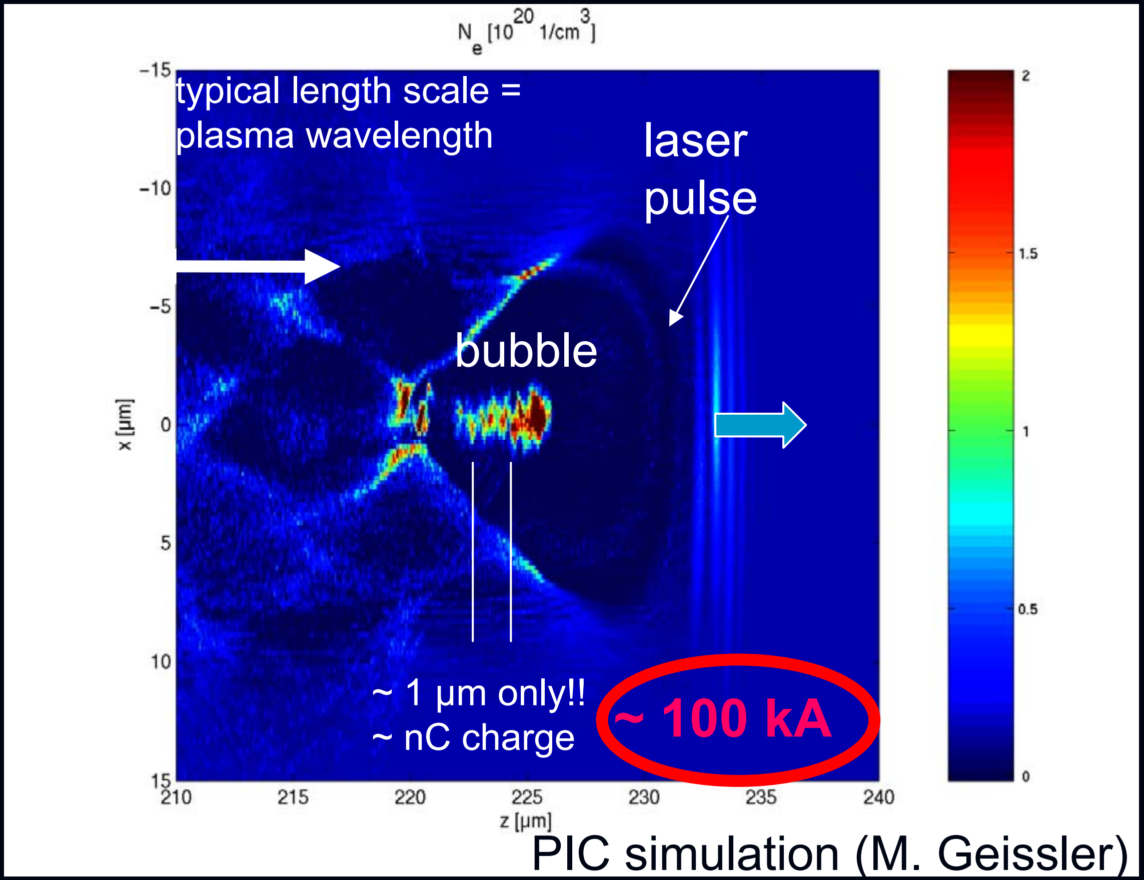


PIC simulation (M. Geissler)

1. laser passes through the plasma → e^- blown out transversely
2. e^- free zone (BUBBLE) behind the laser pulse
3. after ½ plasma oscillation, e^- back to the axis → bubble size ≈ plasma wavel.
4. positive ion background creates strong electric field (up to TV/m)

→ **e^- bunch size << bubble size**

By courtesy of F. Grüner



Goal: 1 nC

1. high density plasma → feeding process more efficient → more electrons

↓

2. shorter laser pulse (< 10 fs) → shorter laser period → smaller bubbles

shorter bubble stems → higher currents: 1 nC in 10 fs

Laser plasma accelerators

shorter laser pulse → lower electron energy

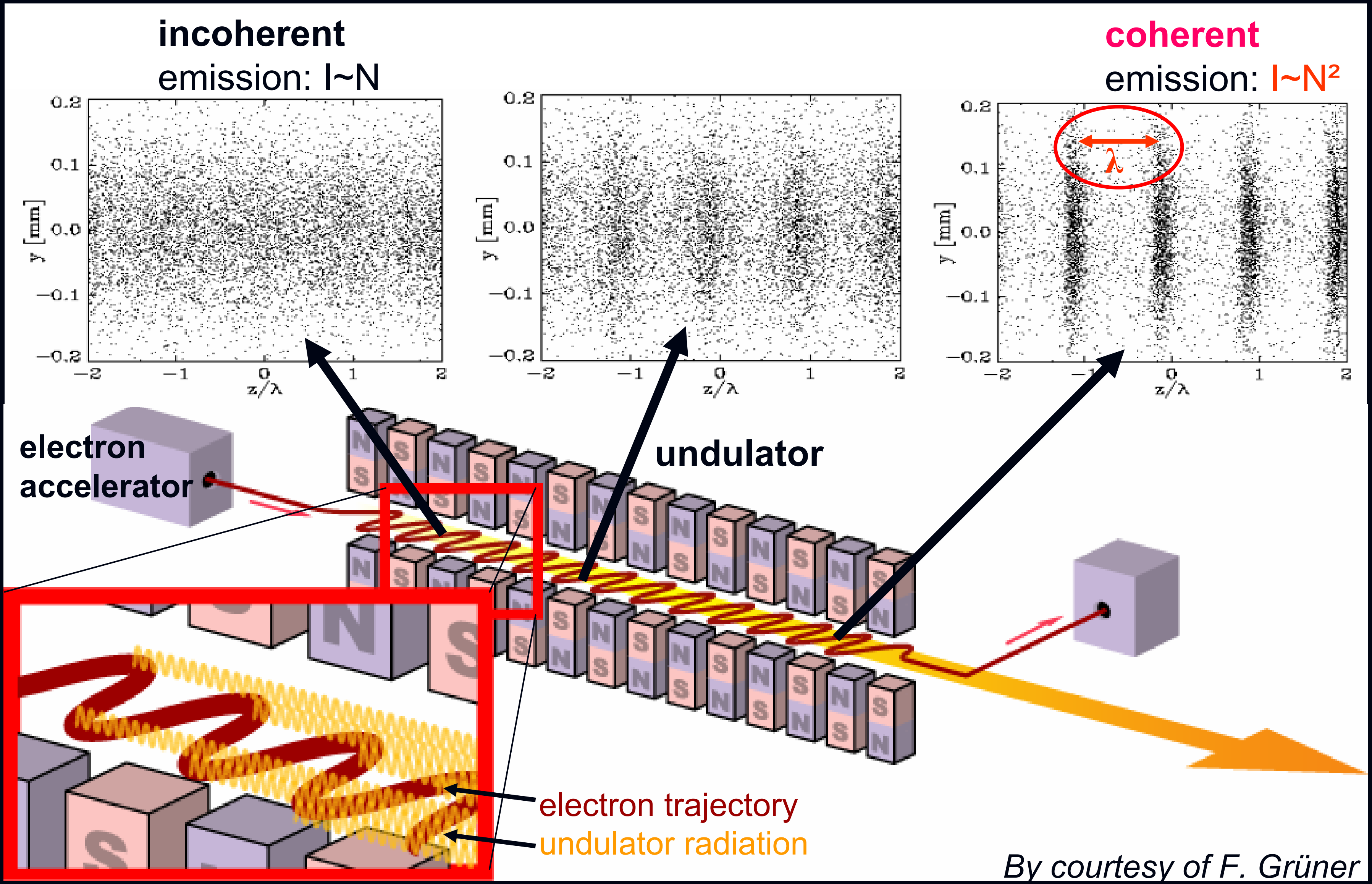
use of capillary

with longitudinal plasma density gradient → laser pulse is forced to gradually increase its diameter

- number and energy spread of bubble electrons are frozen
- energy increases because of bubble fields

	100 MeV	1 GeV
energy spread	1%	0.1%
emittance (mm mrad)	0.1-1	0.1-1

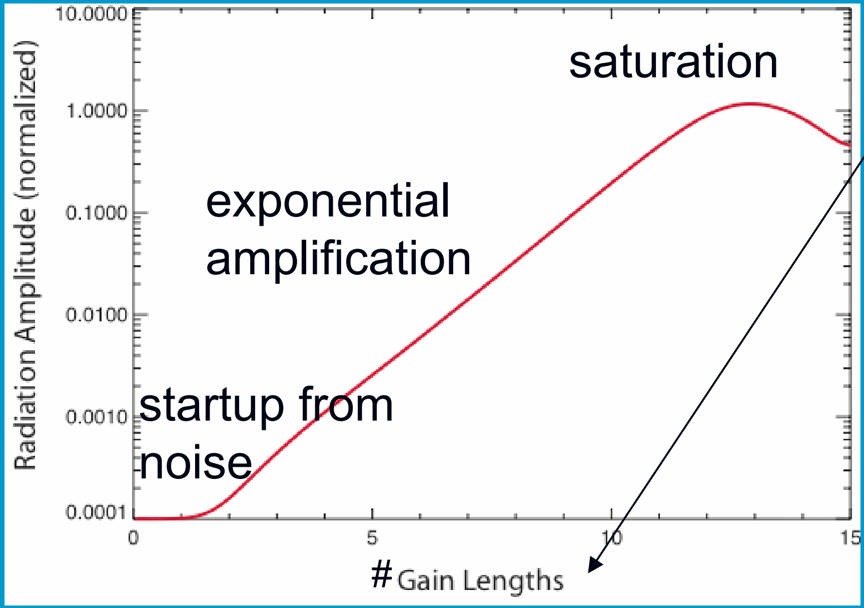
Second step: free-electron-laser (FEL)



- Interaction of spontaneously emitted (incoherent) undulator radiation and electrons
- modulation into MICROBUNCHES separated by distance ~ wavelength of the radiation

How long is the FEL undulator ?

simplest estimate: **ideal** 1D FEL theory
(neglecting energy spread, emittance, diffraction, time-dependence)



- gain length

$$L_{gain,\mathrm{ideal}} = \frac{\lambda_u}{4\pi\sqrt{3}\rho}$$

e-folding of the exponential amplification

- FEL/Pierce parameter

$$\rho \sim \frac{1}{\gamma} \cdot \left(\frac{I}{I_A \cdot \pi \sigma_x^2} \right)^{1/3} \cdot \lambda_u^{4/3}$$

conversion efficiency of electron beam power to FEL radiation and gives upper limit of acceptable energy spread

length along the undulator for having max micro-bunching

undulator length = $L_{sat} \approx (12-25) \cdot L_{gain}$

FEL-wavelength for planar undulator: $$\lambda = \frac{\lambda_u}{2\gamma}\left[1 + \frac{K^2}{2}\right]$$

For having a given energy: a shorter λ_u allows less energetic electrons

⬇

L_{gain} and L_{sat} decrease

→ shorter undulator

⬇

ultra-high current is crucial (> 20 kA)

→ saturation power of FEL radiation: $$P_{sat} \sim \left(\frac{1}{1+\Lambda}\right)^2 (I\lambda_u)^{4/3}$$

→ Pierce parameter large

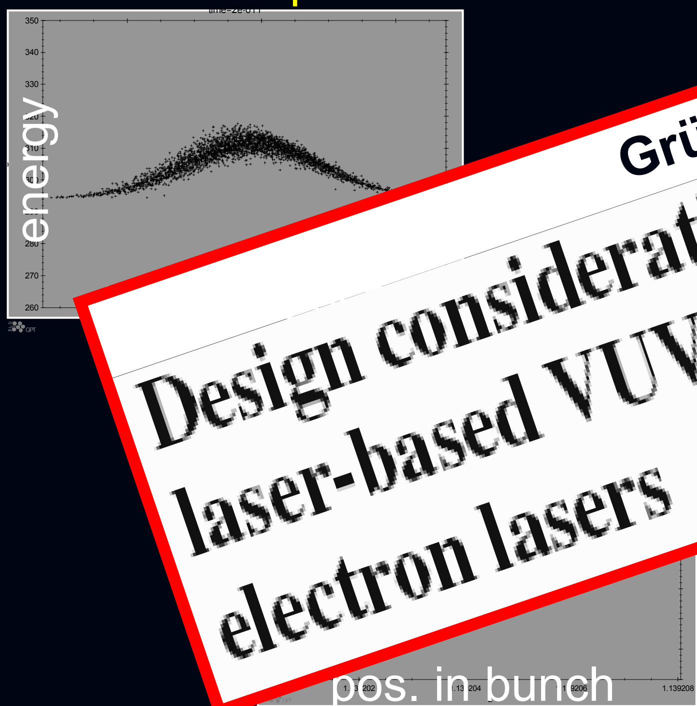
→ correction factor small

10^11..13 photons/bunch, < 100 fs

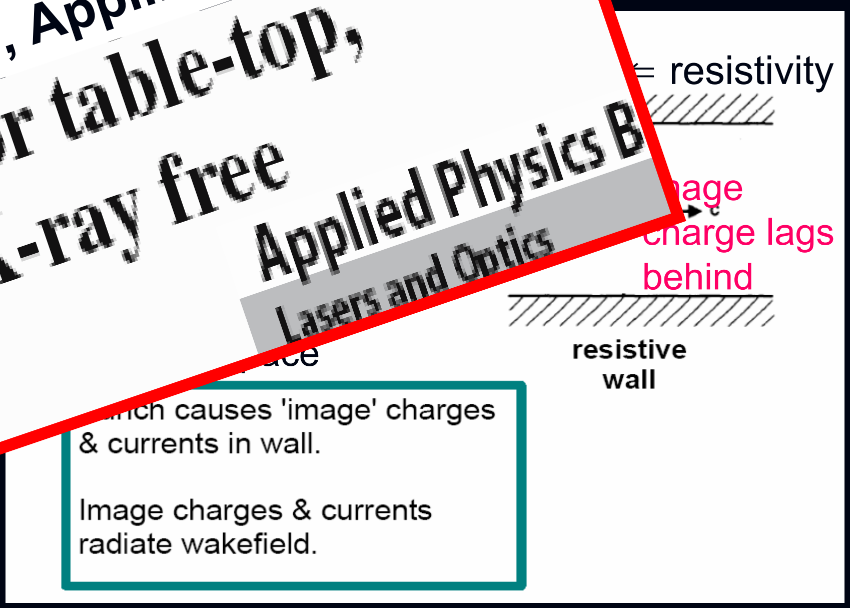
Degradation of the ultra dense electron buches

1. space-charge forces

transverse expansion



2. resistive wall wakefields



Grüner et al, Appl.Phys. B86, 2007

Design considerations for table-top, laser-based VUV and X-ray free electron lasers

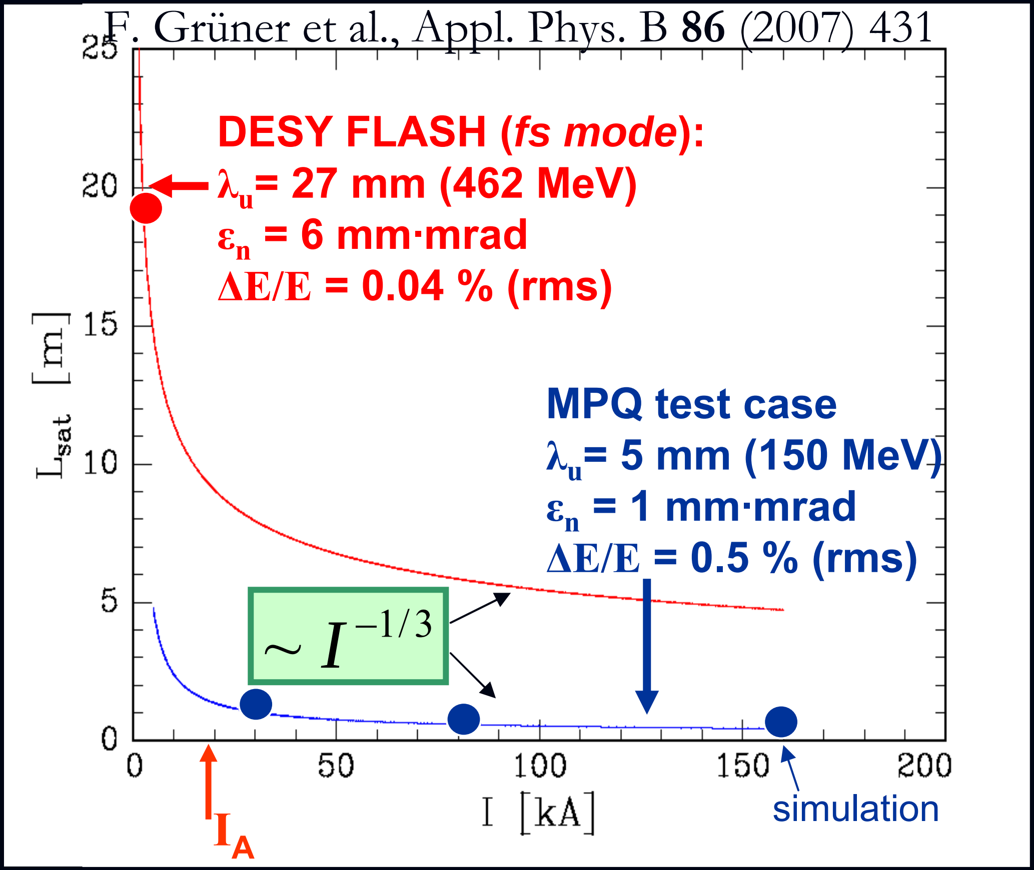
Applied Physics B

Lasers and Optics

Solution: reducing wakefields by increasing gap at same B-field on axis

Table-top FELs driven by ultra-high peak currents

comparison of DESY's FLASH VUV FEL with MPQ test case: both producing 30 nm radiation



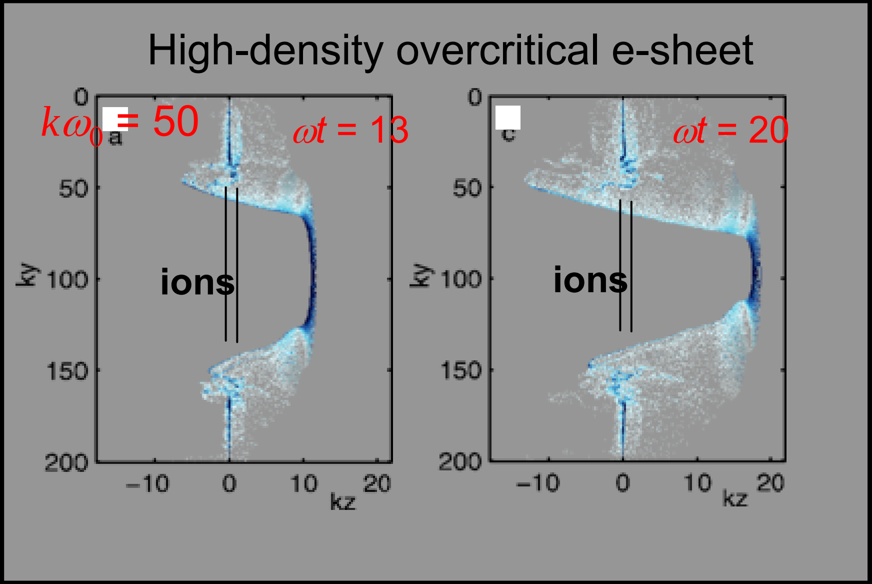
For biomedical applications...

stage 1: 200 TW, 5 fs → 1 nC bunch with ~ 100 MeV, ΔE/E = 5 %

stage 2: 1.2 PW, 100 fs → final 4.7 GeV and ΔE/E = 0.1%

The *MAP* source - **Habs *et al.* (APB, 2008, *in press*)**

Dense laser-driven electron sheets as relativistic mirrors



Production of electron sheet by "driver" laser on very thin diamond-like carbon foils

Ultra-thin foils required: DLC foils extremely stable and transparent act like plasma mirror

Start from solid-state density ($n_e = 10^{24}$ cm^{-3})
not from gas density ($n_e = 10^{19}$ cm^{-3})

Study of the break-out of e-sheets at the ATLAS laser (Munich) and Trident laser (Los Alamos) as first step towards coherent mirror reflection from dense electron sheet

Dense laser-driven electron sheets as relativistic mirrors

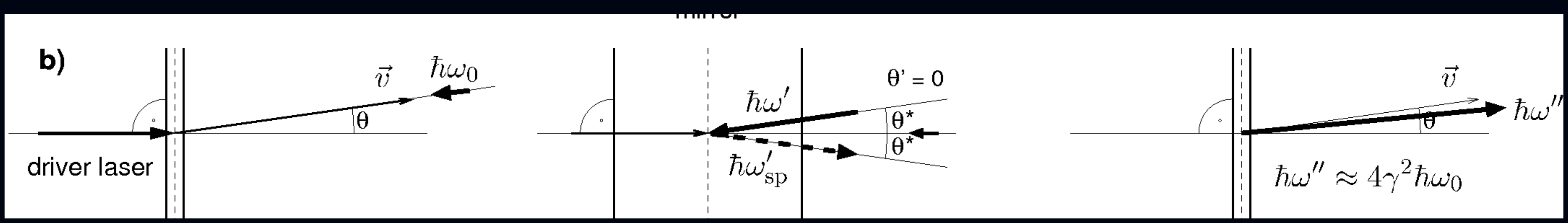
…basics…

"driver" laser intensities with high contrast for producing dense electron sheets

+

propagating "production"-laser for optimum Doppler boost for X-ray production by reflection

injection opposite to electron direction (ICS)



Only if production laser at $\tan\theta = 1/a_L$ we have Doppler boost $4\gamma^2$

Habs *et al.* (APB, 2008, *in press*)

Biomedical applications

MAP and the ESRF

To perform **clinically oriented** developments of
phase contrast imaging techniques

ESRF role: Optimization of the experimental techniques and parameters (source, set-up, detector…) by using synchrotron radiation (→ gold standard radiation)

Application and comparison of different phase imaging techniques (ABI, PBI etc…) in order to find the most suitable technique for compact high brilliant X-ray sources

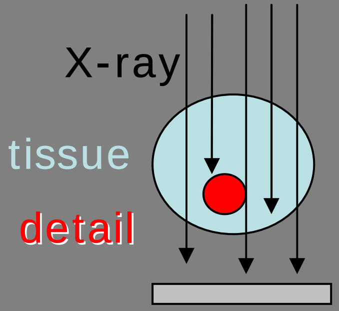
Phase contrast imaging

Contrast mechanisms in X-ray imaging

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

ABSORPTION

β Absorption index

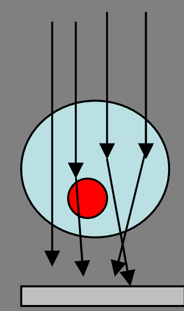


$\mu = 4\pi\beta/\lambda$

absorption

REFRACTION

δ Refractive index decrement



$$\varphi(x,y) = -\frac{2\pi}{\lambda}\int \delta(x,y,z)\,dz$$

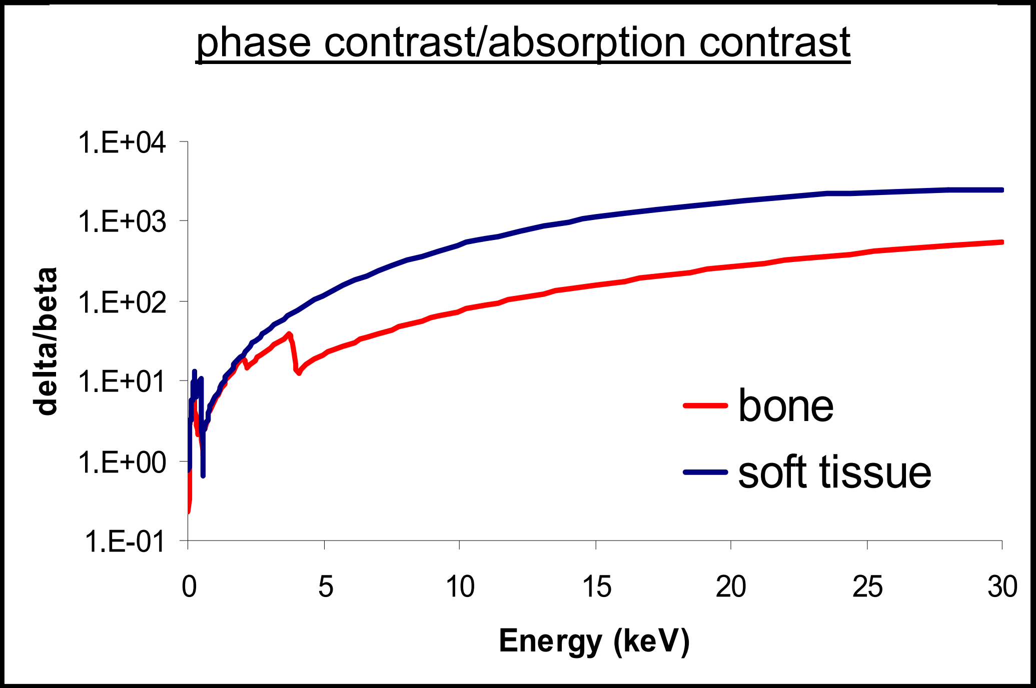
scattering
angles ~μrad

always occur at the same time

Absorption-based radiology

Phase-contrast imaging

Absorption vs Refraction



- Absorption coefficient: $\mu \sim Z^4 E^{-3}$
- Decrement of refractive index: $\delta \sim Z E^{-2}$

$\delta >> \beta$

10^{-6} 10^{-9}

phase effects > absorption

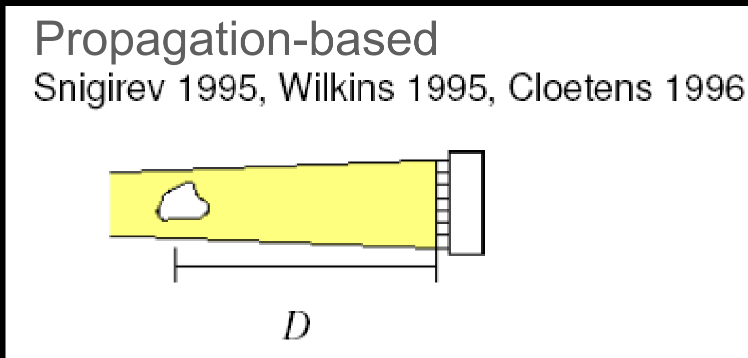
particularly for low Z materials and high energies

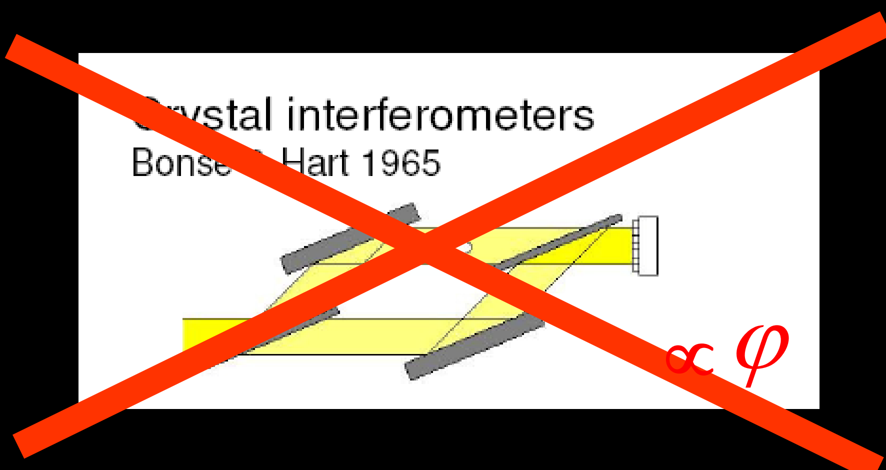
Increase the energy → Absorption contrast ↓

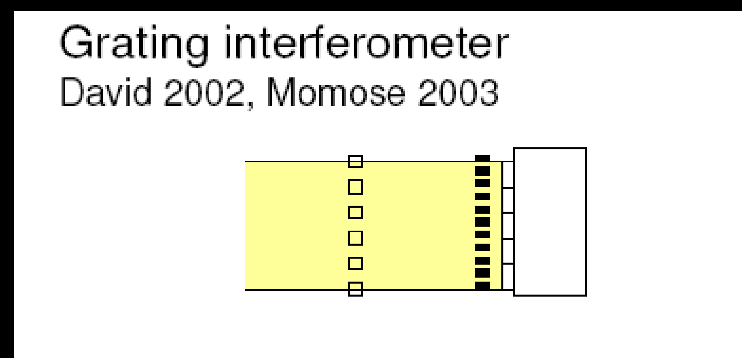
But phase contrast decreases more slowly!

δ → much higher contrast - better sensitivity - at **lower dose**

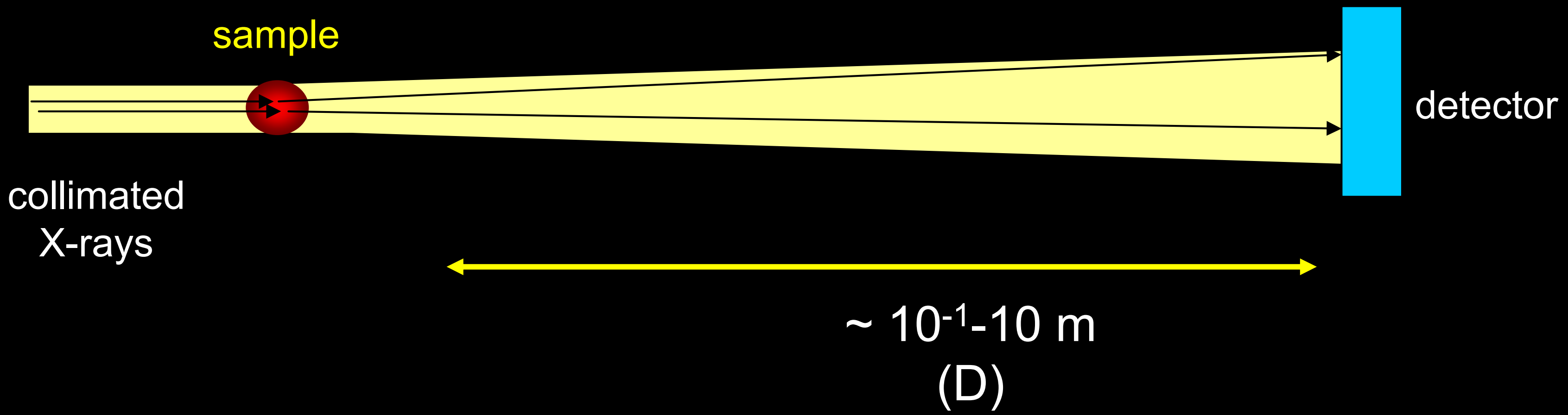
Phase contrast Imaging Techniques







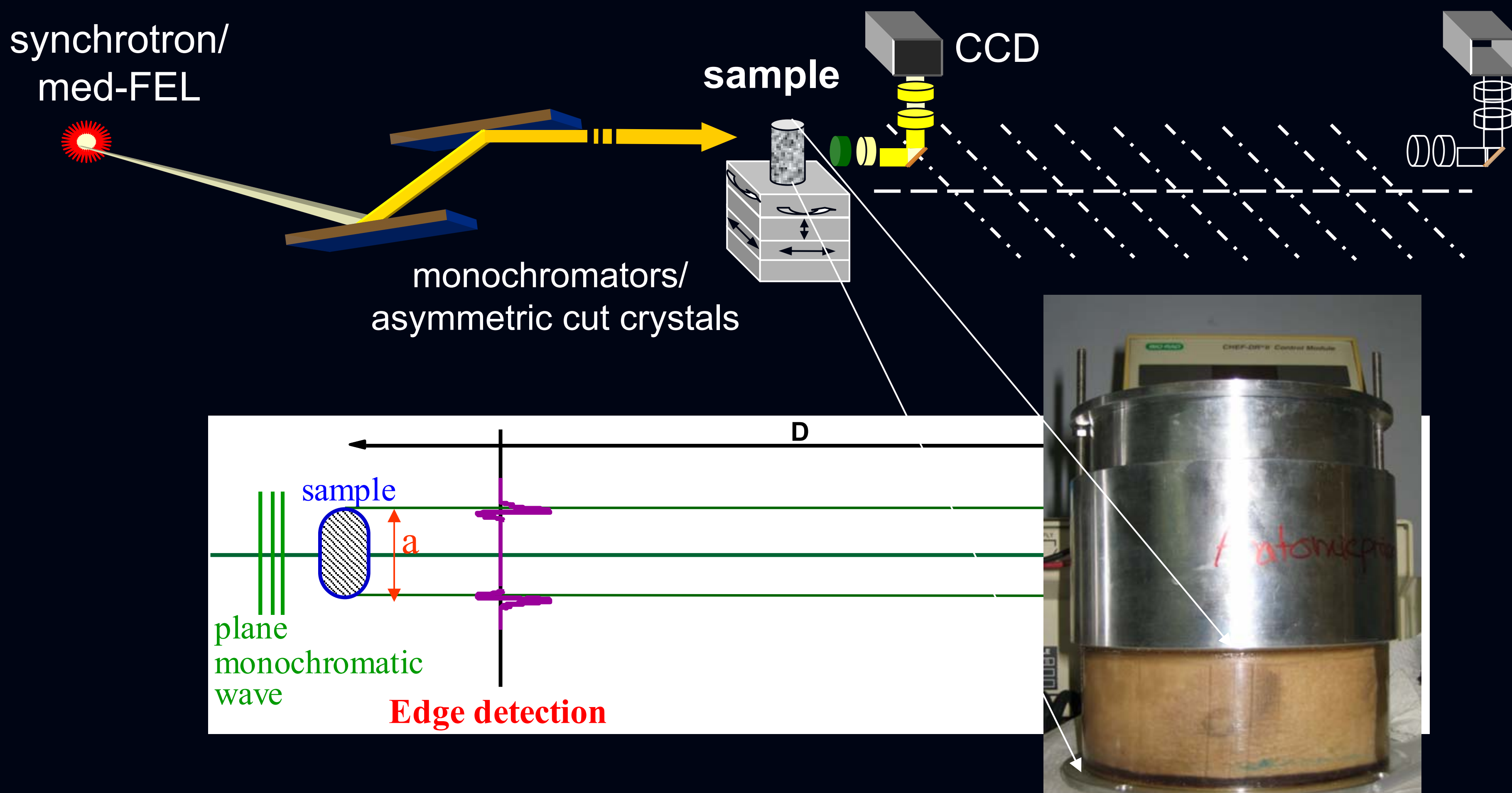
Phase contrast Imaging Techniques



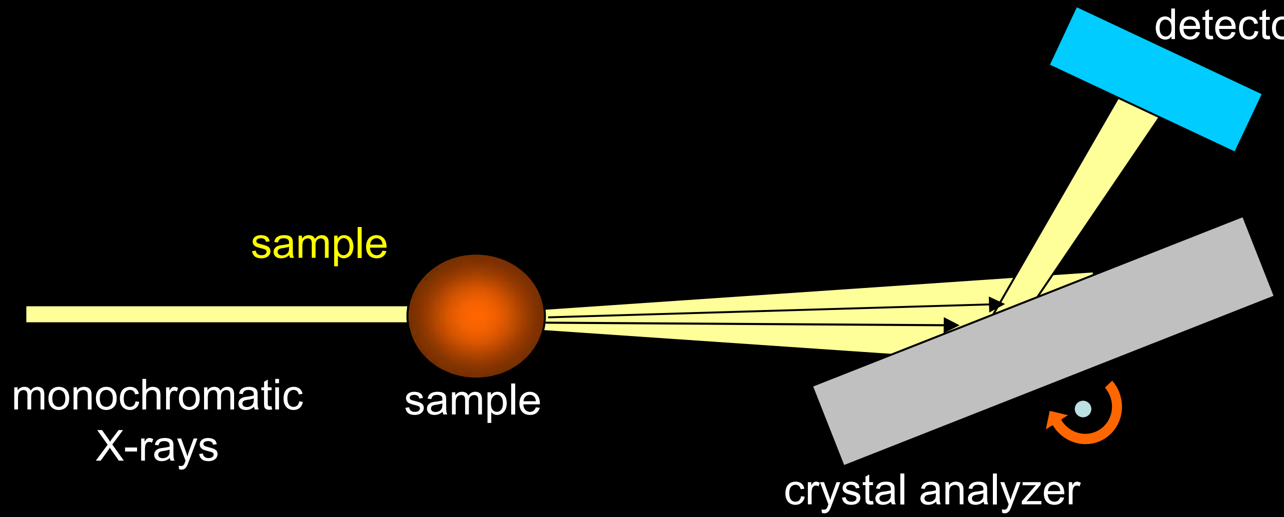
Propagation-based Imaging Technique

Propagation-based imaging

Drift space turns phase distortions into interference fringes → uses of <u>Fresnel diffraction</u>

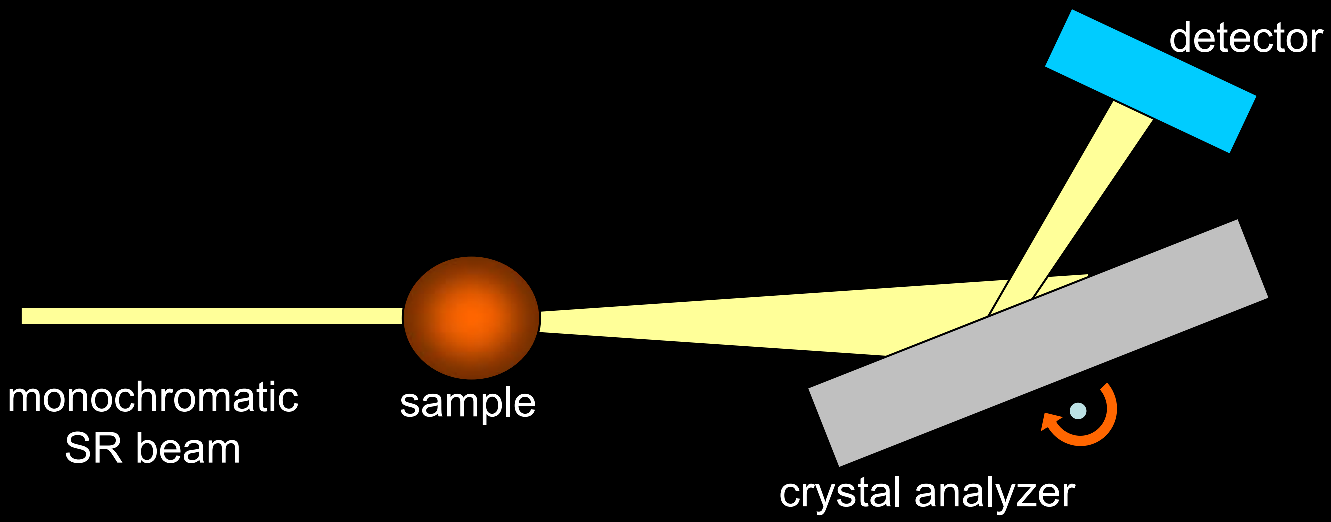


Phase contrast Imaging Techniques



Analyzer-based Imaging Technique

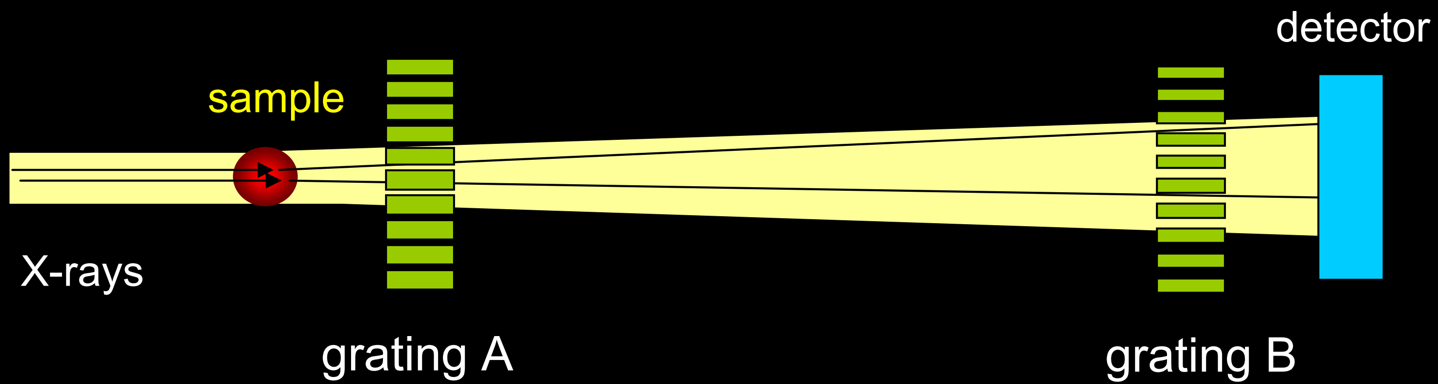
Analyzer-based imaging technique



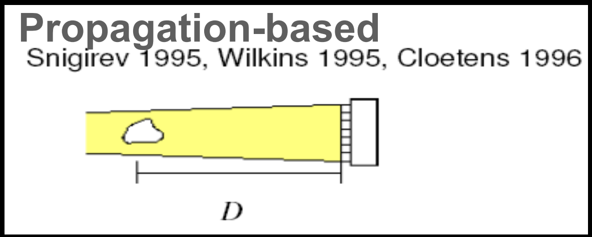
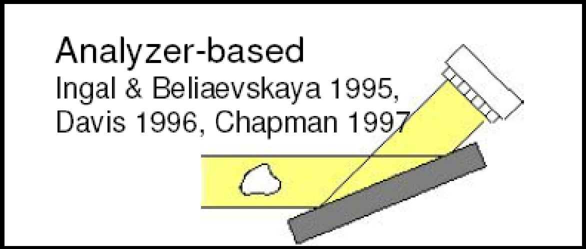
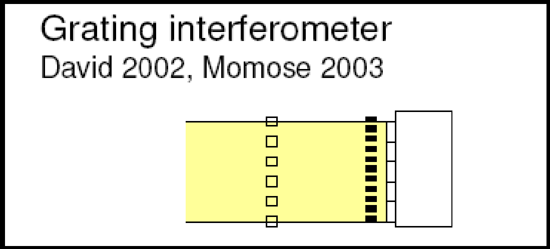
- Analyzer crystal acts as an angular filter
  of the radiation refracted and scattered inside the object

- filter function given by analyzer rocking curve (RC)
  (typical angular acceptance: FWHM ~ few microradians)

Phase contrast Imaging Techniques



Grating interferometer technique

Propagation-based Im.	Analyzer-based Im.	Grating-based Im.
		
$\propto \nabla^2 \varphi$ (wavefront phase)	$\propto \nabla \varphi$	$\propto \nabla \varphi$
needs high spatial coherence	needs high temporal coherence and parallel beam	can use divergent and polychromatic beams

Which phase contrast technique for MAP biomedical applications?

PBI

energy width $\Delta E/E \approx 1\%$ required

photon flux: $5 \cdot 10^{10}$ / **s**

→ well suited for table-top med-FEL (full **5** keV design study: $1.2 \cdot 10^{11}$ photons/**bunch**)

What is needed to move to clinics?

- Experimental and theoretical development of the different phase contrast techniques and their comparison (Collab. F. Pfeiffer, PSI)

  - For finding the best technique for a given tissue

    `best` = most sensitive and most experimentally convenient and easiest

- Quantitative analysis of phase contrast images
  - separation of absorption – refraction – scattering contributions to image contrast
  - comparison of the different mathematical algorithms - implementation of a code

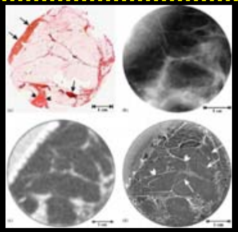
- Development of imaging modalities:
  - Tomosynthesis for high resolution phase-contrast imaging

- Multi-techniques approach: phase-contrast imaging combined to small-angle X-ray scattering (SAXS)
  - to supplement ABI results and help in the refraction image interpretation

MAP project – biomedical applications

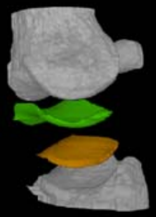
Biomedical applications:

Low-dose mammography



- Early detection of breast cancer

A. Bravin's talk September 11 at 17h



In-vitro and *in-vivo* cartilage studies

- Early detection of osteoarthritis and metal implant healing evaluation

What's new?

Clinical orientation

- Focus on dense breast tissue and whole breast specimens (~15 cm sample diameter)

- High resolution CT imaging for cartilage matrix components and architecture visualization

Articular cartilage imaging

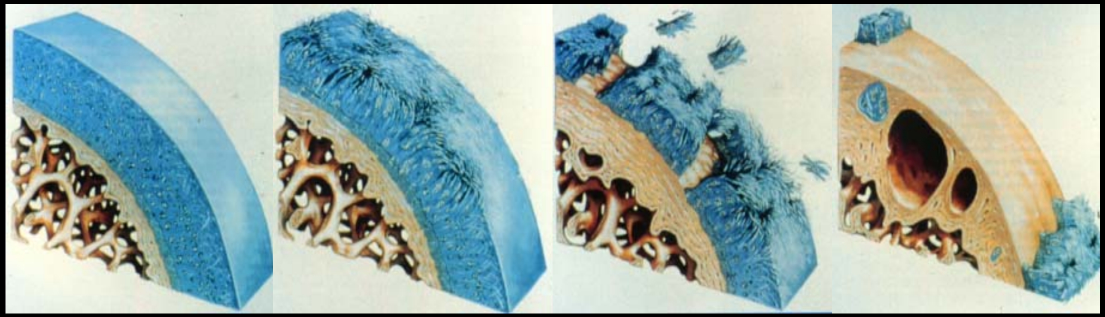
Why focusing on cartilage joint diseases?

Osteoarthritis (OA) is one of the leading causes of disability;
people with OA usually have joint **pain** and **limited movement** (stiffness)

12% of the population in the seven major pharmaceutical markets
(USA, Japan, France, Germany, Italy, Spain, and the UK)
(http://www.marketresearch.com/map/prod/843319.html)

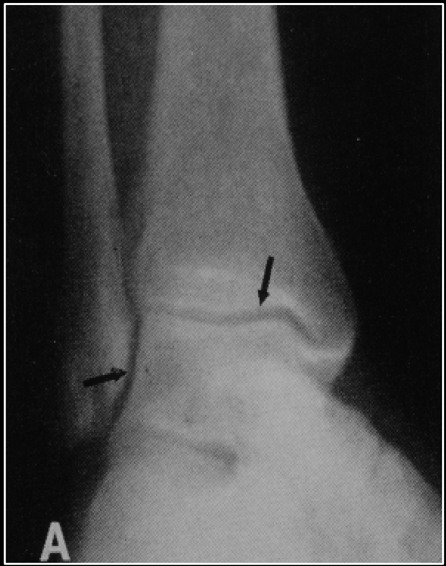
Osteoarthritis (OA) is a joint disease mostly affecting the **cartilage.**

Cartilage degeneration process – Collins grading system (Collins, 1949)

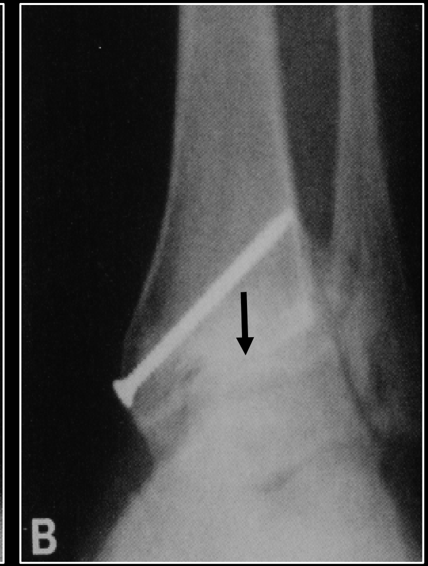


As OA presently has **no cure**:
focus on **treating the disease symptoms** with minimal side effects

Conventional radiology limitations



Normal Ankle



Osteoarthritic Ankle

Conventional radiographs do not show cartilage;
joint space narrowing
is evaluated by proximity of bones

contact between bones

degeneration of cartilage

In conventional radiography, OA is detected only at too advanced disease stages

TOO LATE!

Need of a high resolution, non-invasive diagnostic technique allowing…

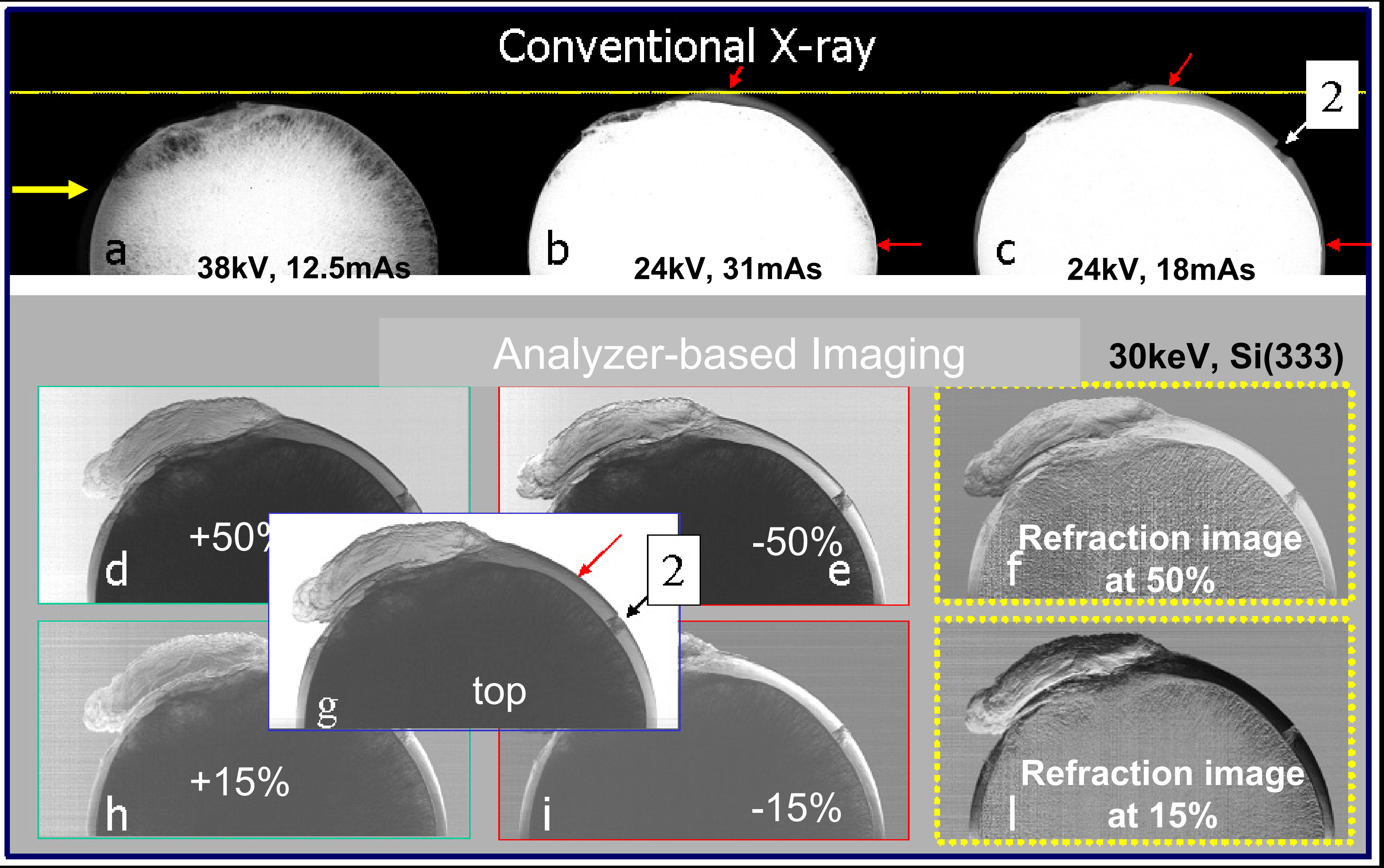
- for the early detection and the follow-up of OA
- the evaluation of drug efficacy
- the implant healing assessment

Selected results

Human femoral head (hip)

ABI vs conventional radiography

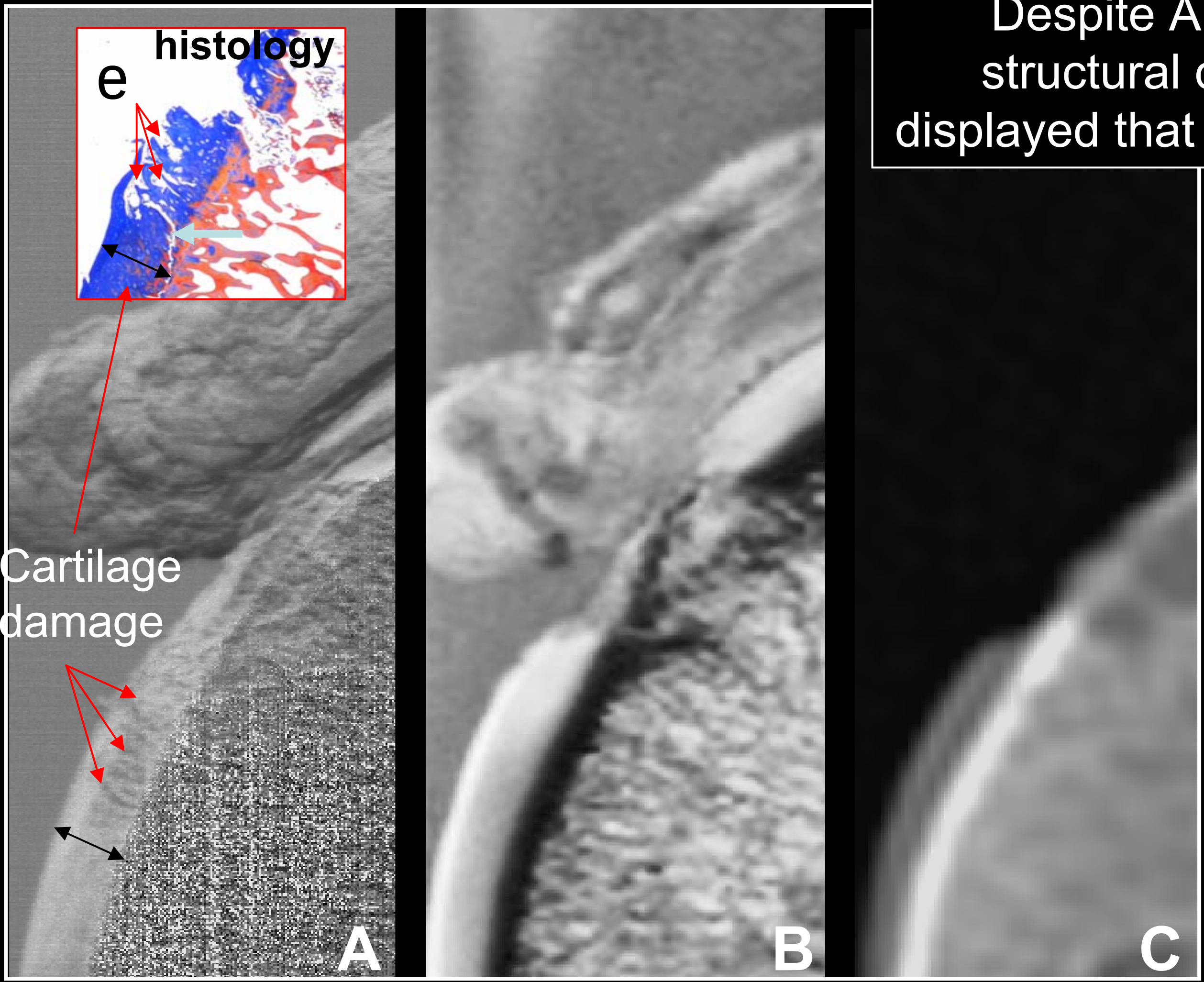
Cartilage tissue is invisible!



A. Wagner,…P. Coan, A. Bravin, J. Mollenahuer, *SPIE Medical Imaging* (SPIE, 2005), Vol. 5746, p. 542-549

HIP - ABI vs conventional techniques

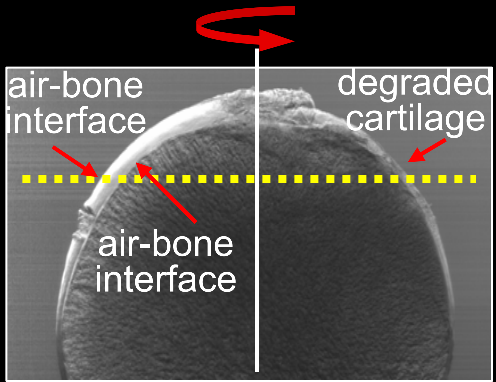
Despite A is a projection image structural damage of cartilage is displayed that is invisible in MRI and CT



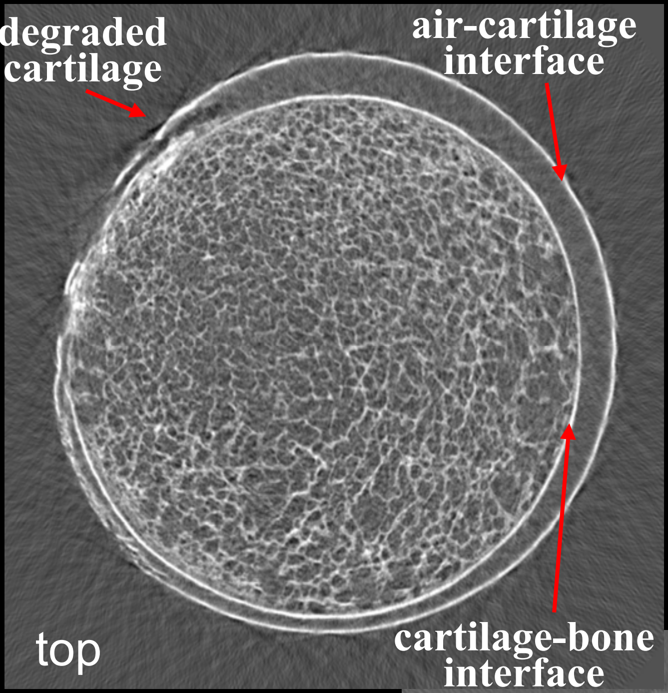
ABI (Refraction Im.) MRI Conventional CT

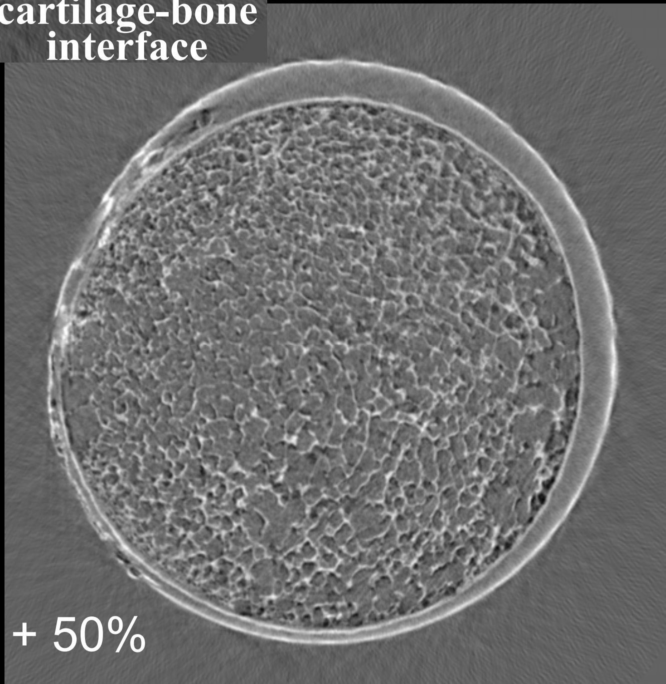
A. Wagner… P. Coan, A. Bravin, J. Mollenahuer *et al*., "Options and Limitations of Joint Cartilage Imaging: DEI in Comparison to MRI and Sonography," Nucl. Instr. Meth. A **548**, 47-53 (2005)

High energy tomography (CT) with ABI



ABI projection -50%





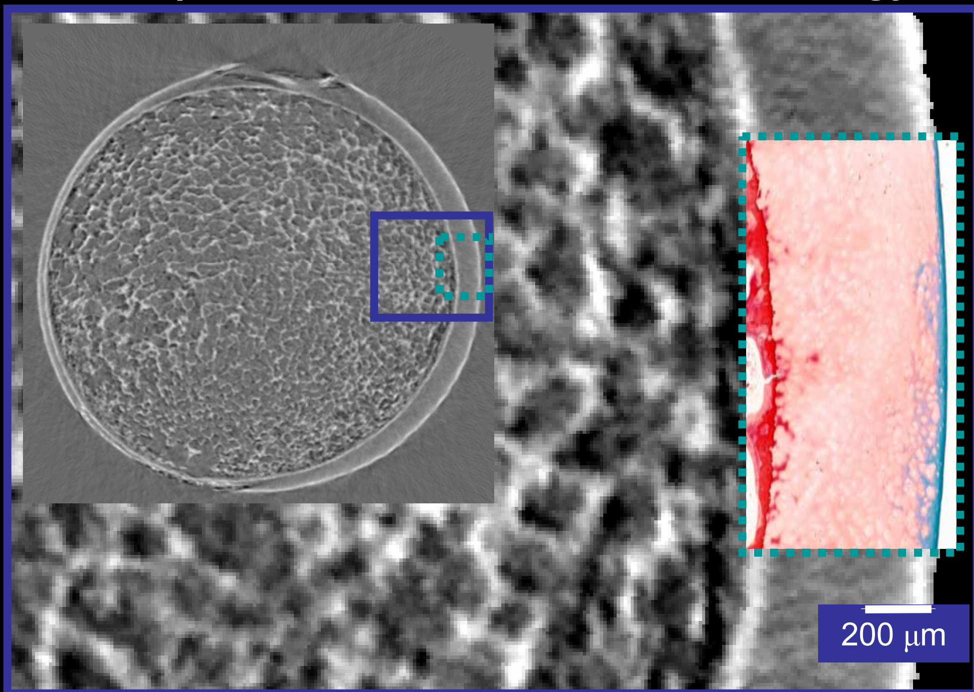
Human hip
50 keV
Si(333)

- **Interfaces highlighted**
- **Trabecular meshwork well defined**

<u>Coan et al, EJR, 2008, *in press*</u>

HIP ABI-CT vs histology

Comparison of CT ABI and histology

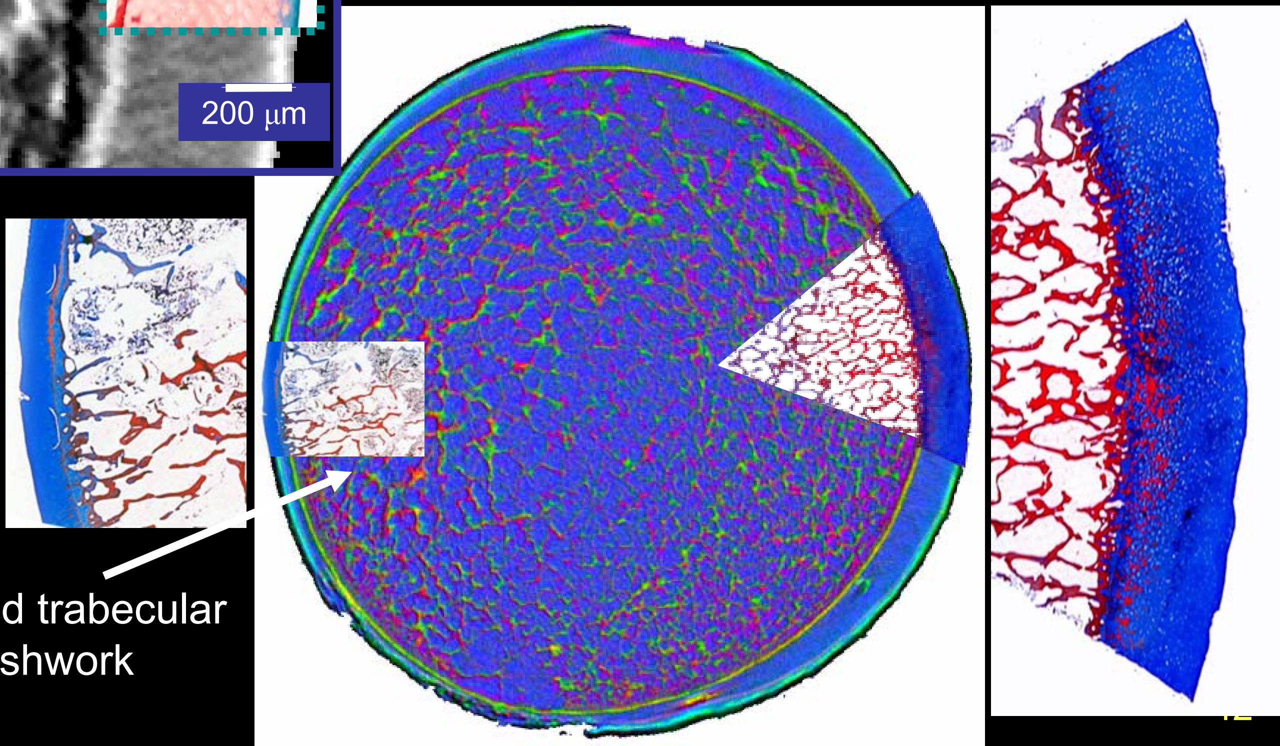


ABI-CT images perfectly match histological cuts

Human hip

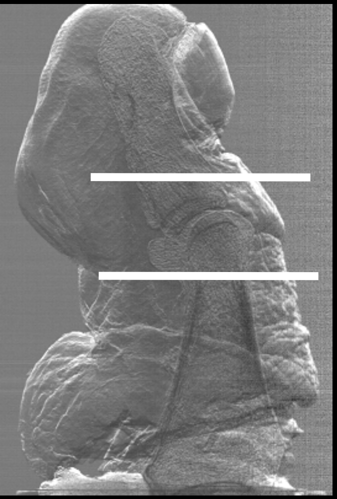
50 keV Si(333)

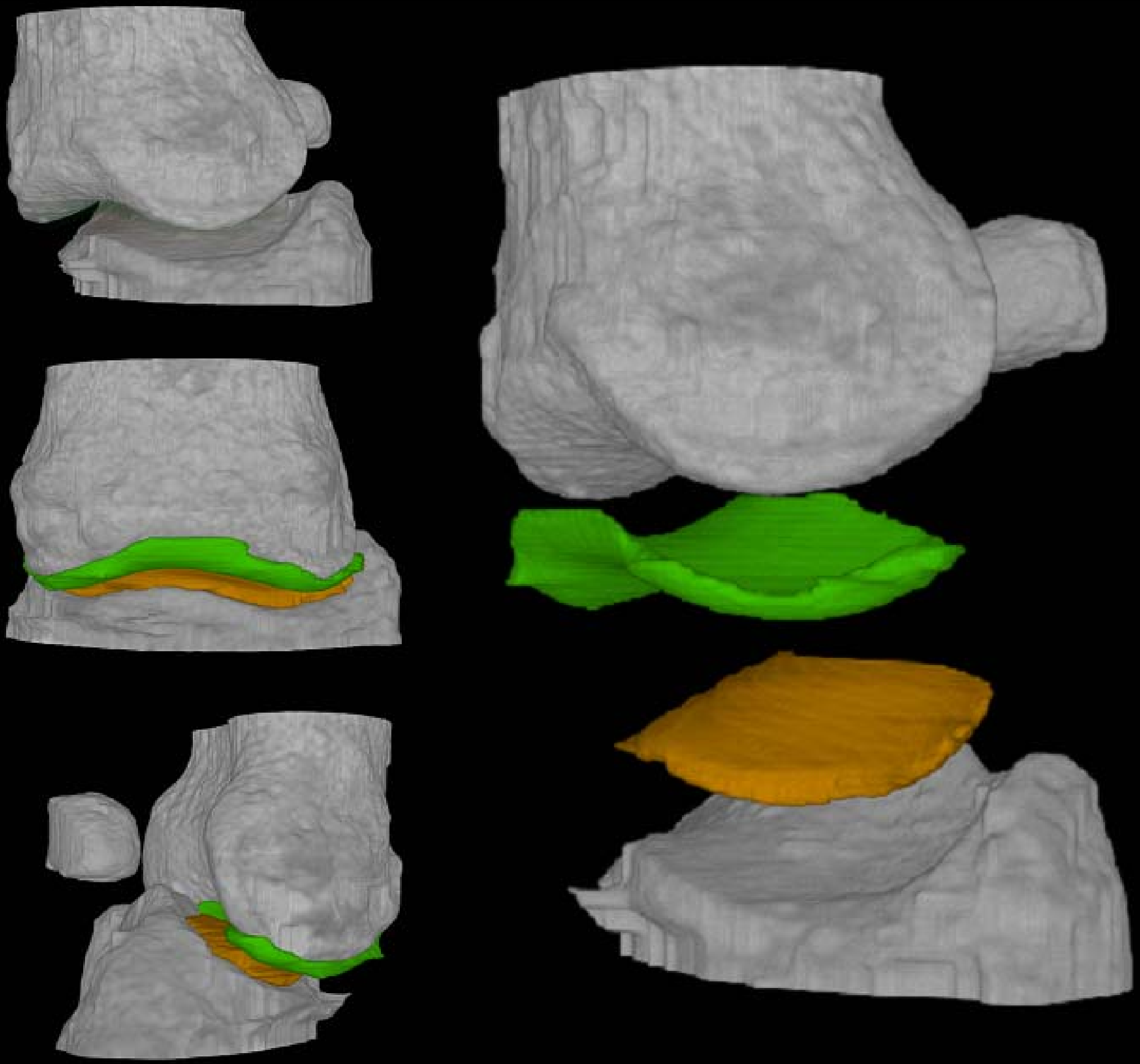
-50%



damaged trabecular meshwork

3D rendering from ABI CT – Human big toe joint





Coan et al, EJR, 2008, *in press*

First MAP experiments at the ESRF

Conclusions

High potentiality of phase contrast techniques has been largely proven!

Mainly at synchrotron facilities!

Clinical mission

Optimization of PhC modalities

Compact X-ray sources

- Strong synergy between physicists, physicians and computing engineers
- Collaboration between the experimental and theoretical group working on phase contrast imaging
- Other collaborations?

Thanks for your attention

At the ESRF…

Dr. A. Bravin

P.C. Diemoz

In Munich…

X-ray source

Prof. D. Habs

Dr. F. Grüner

Biomedical applications

Dr. C. Glaser

Dr. T. Schneider

Prof. M. Reiser