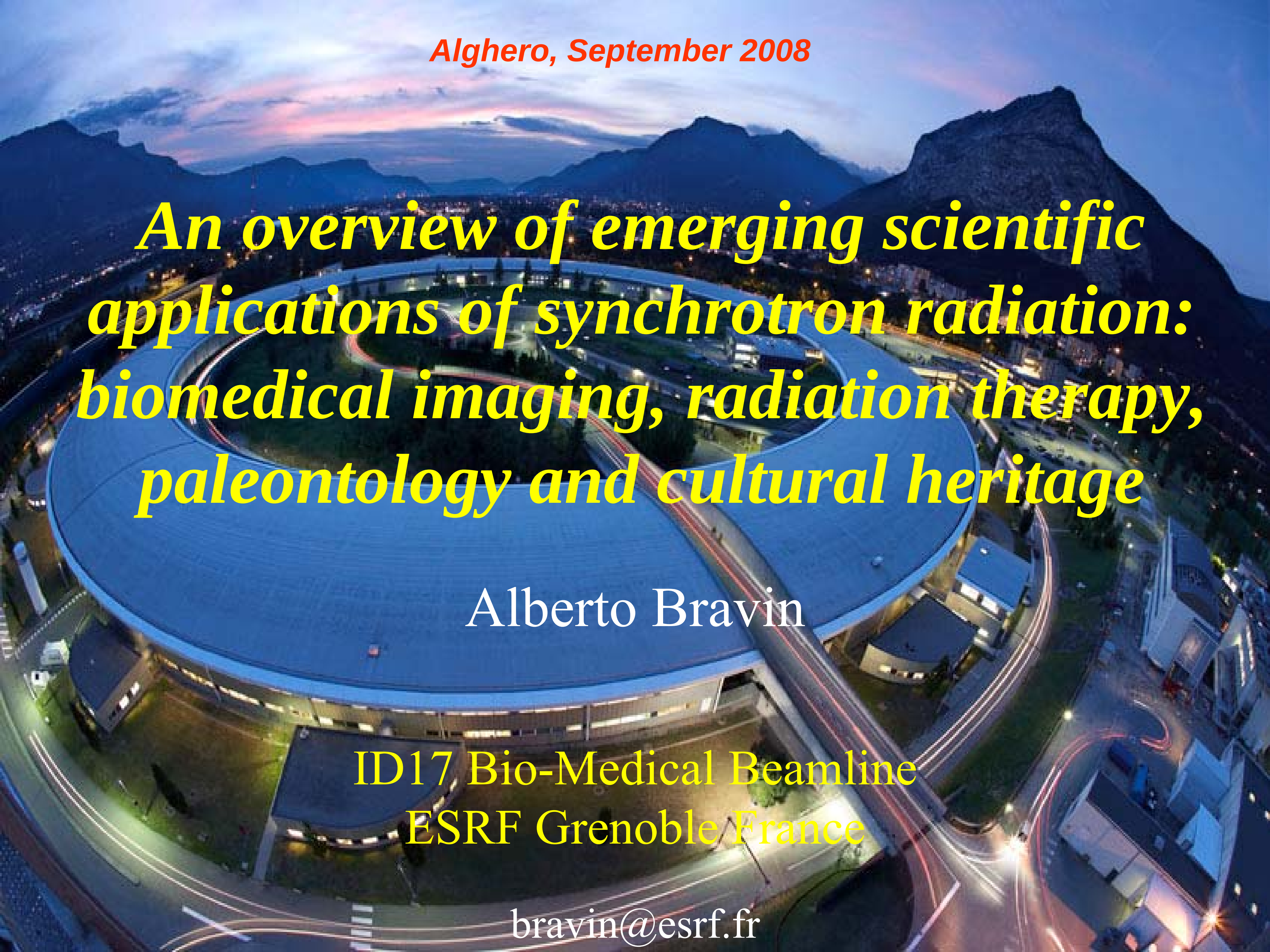

Alghero, September 2008

An overview of emerging scientific applications of synchrotron radiation: biomedical imaging, radiation therapy, paleontology and cultural heritage

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ESRF Grenoble France

bravin@esrf.fr

Outline

- X ray imaging:
  - Biomedical applications
  - Paleontology
  - Cultural heritage
- Radiotherapy with SR:
  - Stereotactic Synchrotron Radiation Therapy
  - Microbeam and minibeam radiation therapy
- Reference parameters for clinical and scientific applications

Imaging

Bio-Medical beamline (ID17)

Mission: **Clinically-oriented** research:

- Medical imaging
- Radiobiology
- Radiation Therapy
- Other (5%)

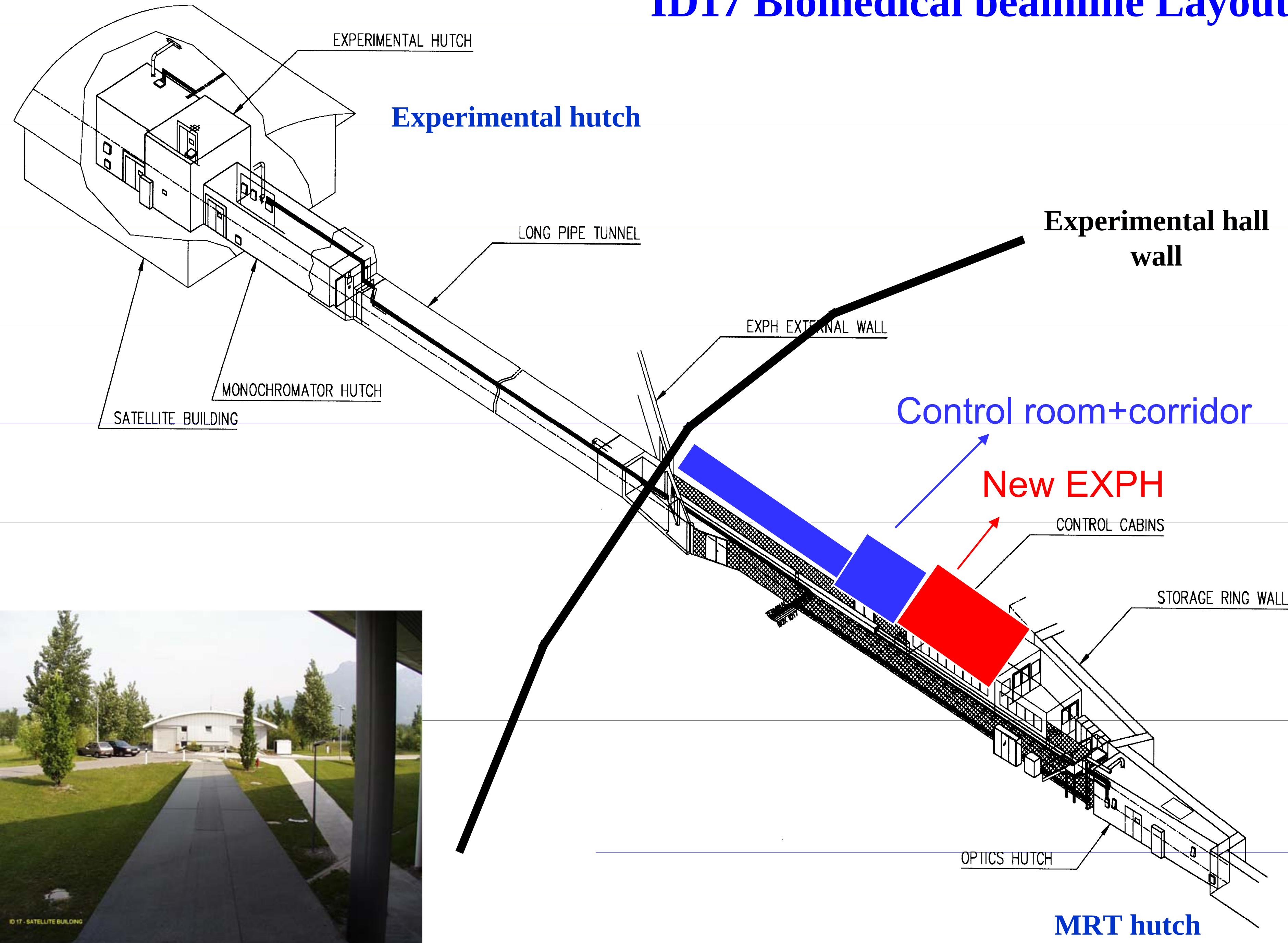
Clinically (=patients) oriented:

• Preclinical research contributing to the clinical medicine in hospitals (testing new drugs, contrast agents, finding origin of illness, measure physiological parameters, study the effect of radiation on cells/tissues etc)
• Perform clinical research when it is only possible with SR (angiography, radiotherapy)
• Develop science which could be applied in clinics at compact SR sources

Preclinical research is done in phantoms, cells, animal models

3 teams working together: ID17 staff, Biomedical Facility (biologists, animal/lab technicians)+ CHU/INSERM/UJF team

ID17 Biomedical beamline Layout



Why SR light for imaging?

Intense, collimated and polarized source of X-rays in a wide energy range (1- 100 keV)

- Monochromaticity (no beam hardening, quantitative projection and CT, K-edge imaging, energy optimisation with sample, dose reduction…)
- Collimation (highly reduced scattering on the images), parallel beam (no cone beam effects)
- Collimation+ small source (coherence): phase contrast imaging
- (Linearly) Polarized (reduced scattering)
- Flexible setup: combination of different techniques (CT + fluorescence + EXAFS….)

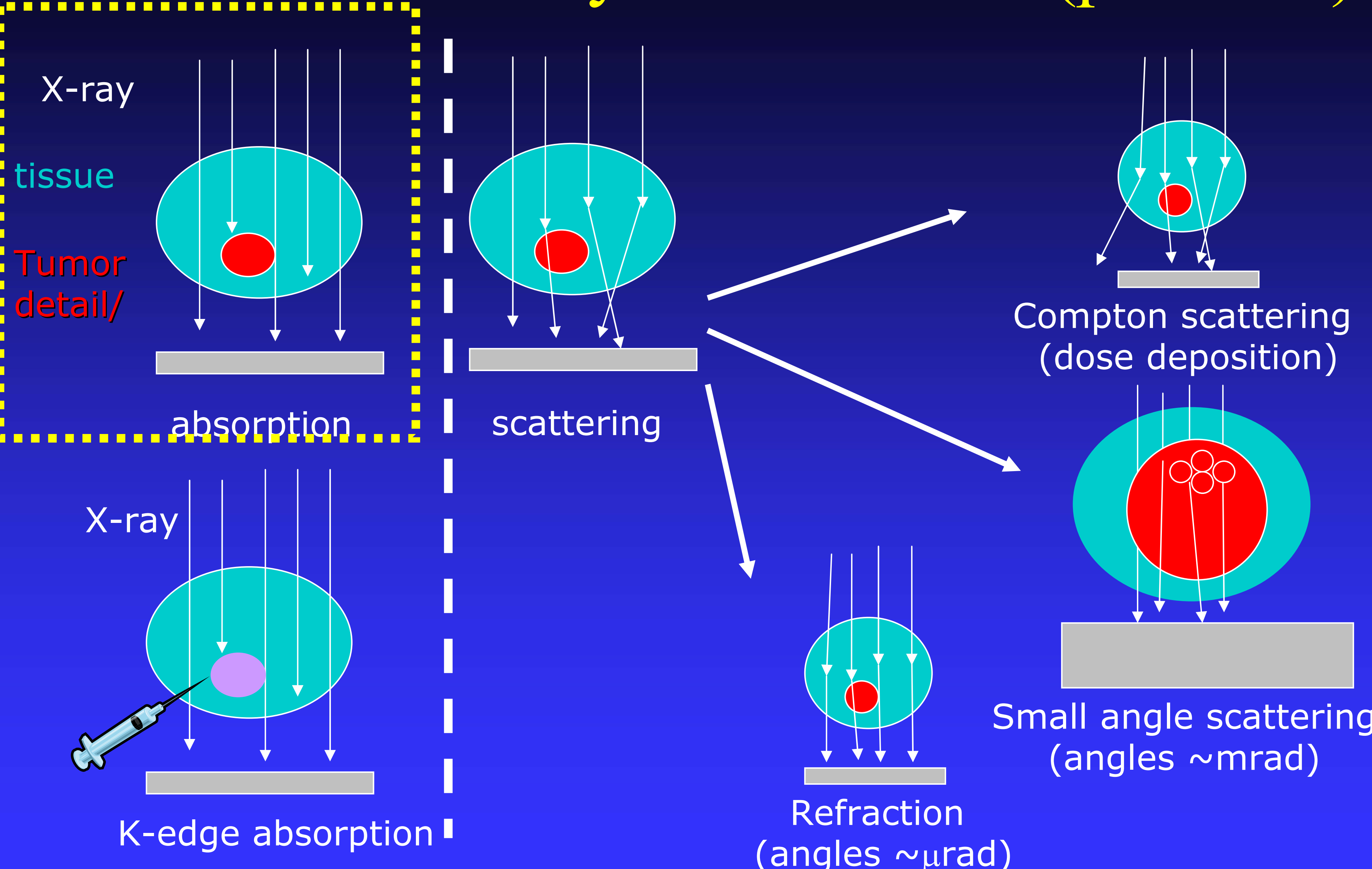
Imaging

Biomedical imaging

Paleontology

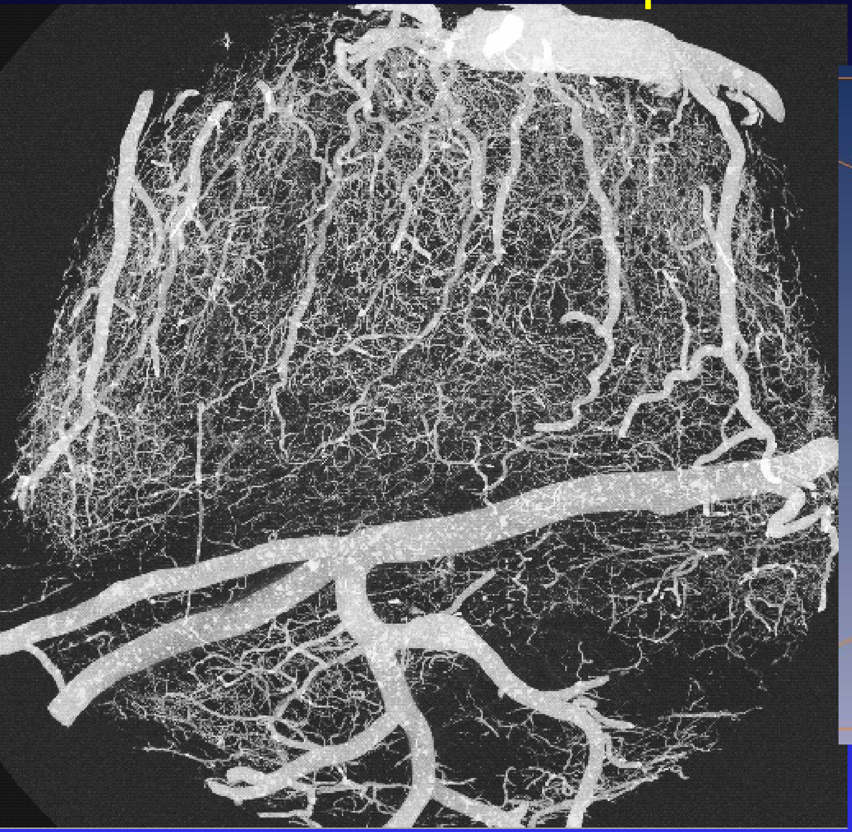
Cultural heritage

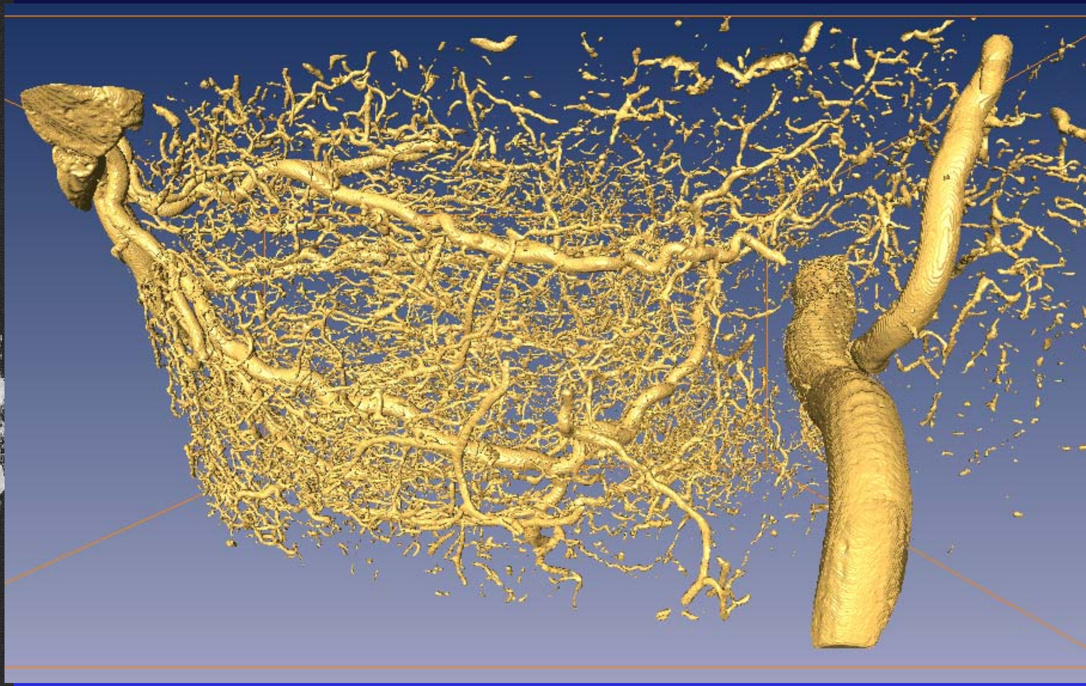
Interaction of X-rays with tissues (pictorial)



http://detserv1.dl.ac.uk/Herald/xray_history.htm

Cortical brain imaging: Characterization of brain vascular network and transport after injection of barium





Sample size: 1.5x1.5x1 mm^3

frontal cortex: y-z plane

3D iso-surface frontal cortex
y-z plane

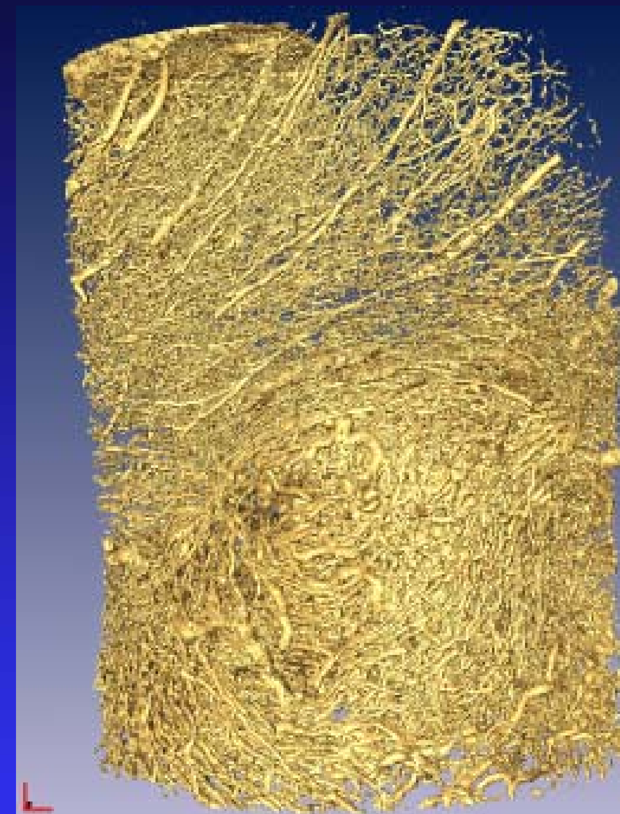
Rat cortical brain. Barium (600 $mg*mL^{-1}$), 20 keV in absorption; voxel size = 1.4 μm.

F. Pouraboué et al. J. of Microscopy, Vol. 215, August 2004,139–148

20.5 keV pixel 1.4 micron

bar= 0.1 mm

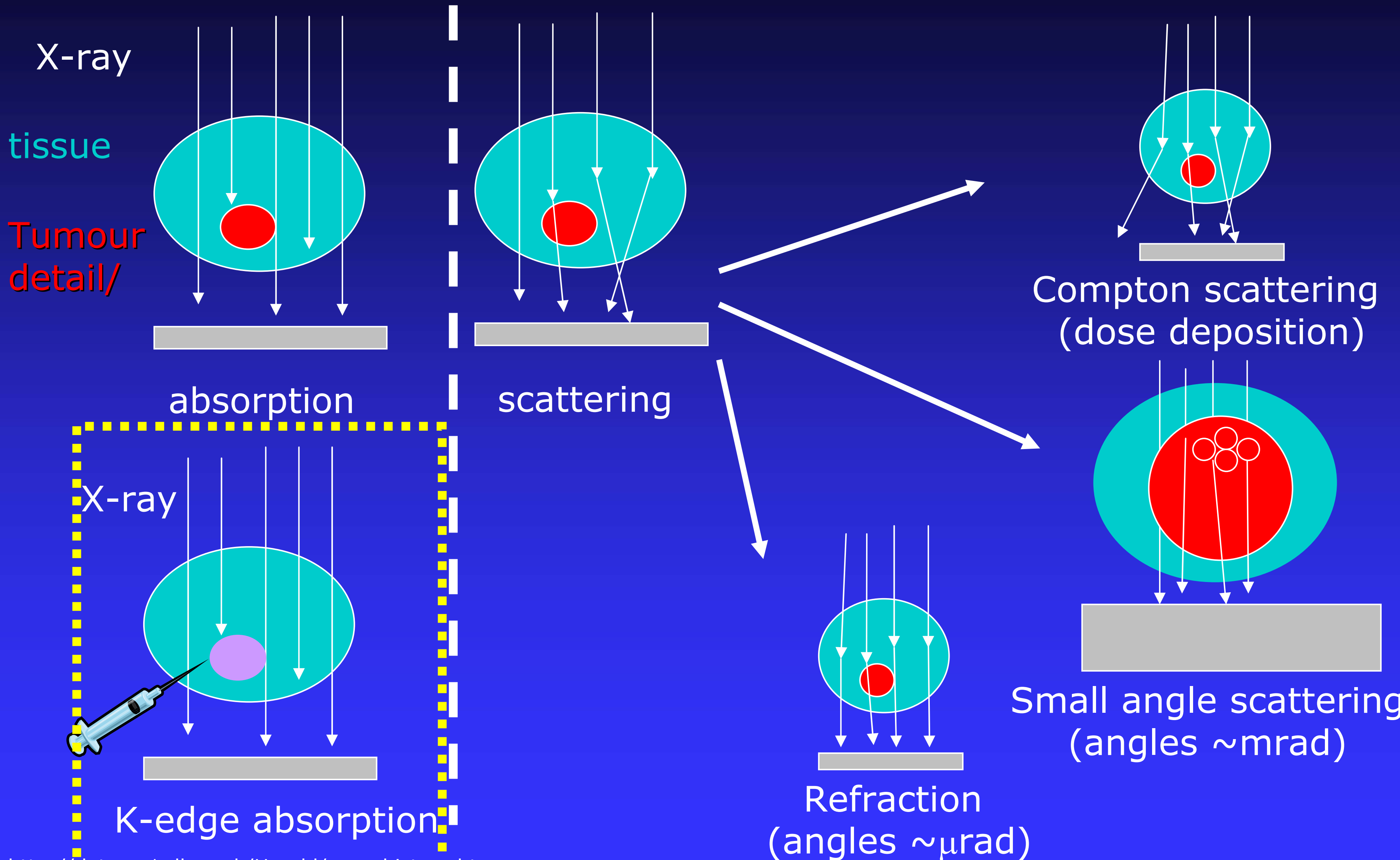
Monkey cortical vascular network



Implanted tumor cortical vascular network in rat cortex

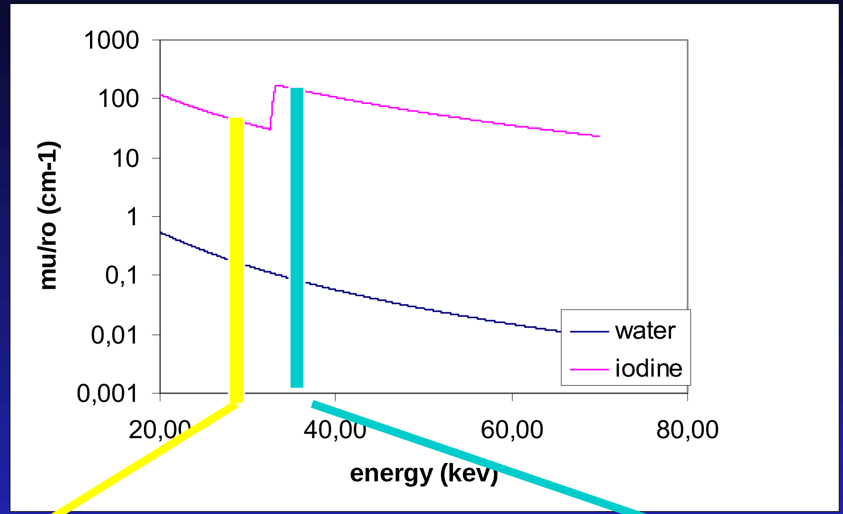
L. Risser et al. J. Cereb. Blood flow and Metabolism, 2006

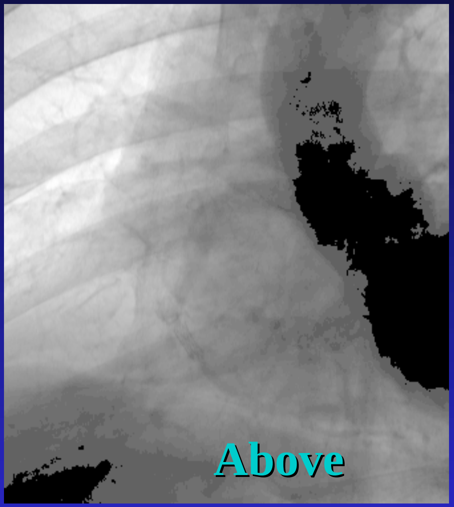
Interaction of X-rays with tissues (pictorial)

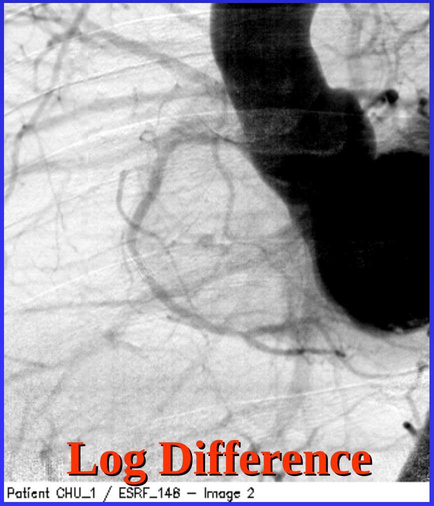


http://detserv1.dl.ac.uk/Herald/xray_history.htm

K-edge Subtraction Imaging







H. Elleaume et al. Phys. Med. Biol. 2000 45: L39; B. Bertrand et al. Europ. Heart J., 2005 26: 1284

Dynamical angiography for brain vascular disease detection

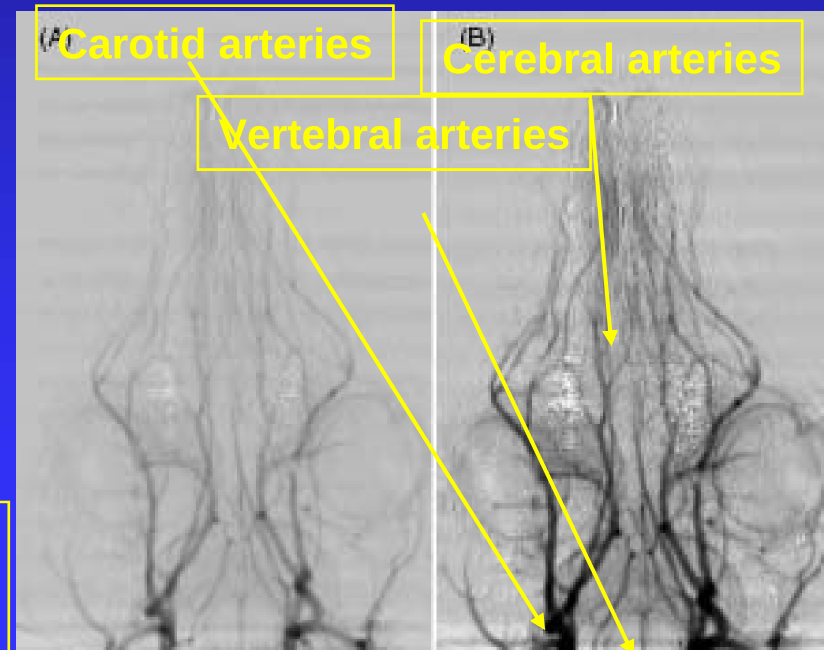
- Conventional digital subtraction angiography: gold standard for brain vascular disease diagnostics (stroke, infartus, aneurysm etc). Intra-arterial catheterization (femoral artery): 1% cases of permanent neurological damages. No routine
- Monochromatic K-edge subtraction imaging: much higher sensitivity →intravenous injection

In-vivo rabbit brain imaging

Conventional (Philips BV IA)

Intra-carotid injection (4 ml Iomeprol @350 mg/ml)

SR K-edge subtraction

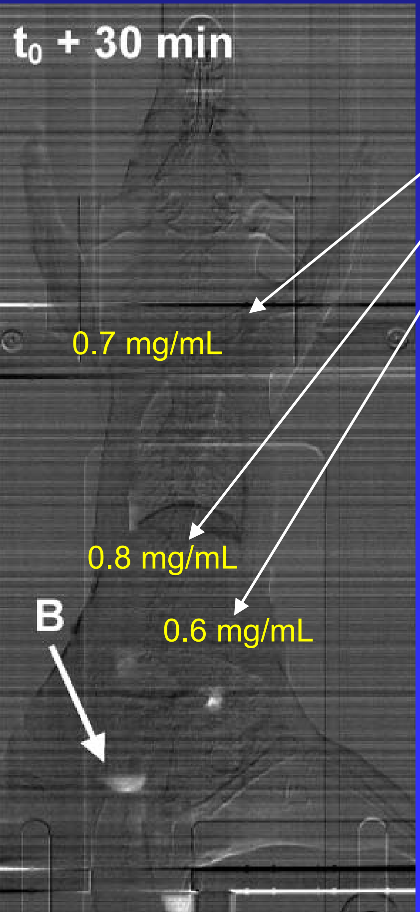


33 keV; intravenous 1.5 ml Iomeprol

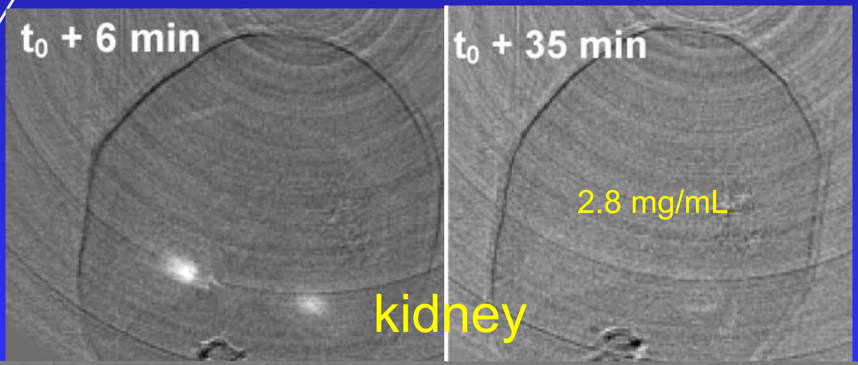
M.E. Kelly et al. Phys. Med. Biol. 52 (2007) 1001

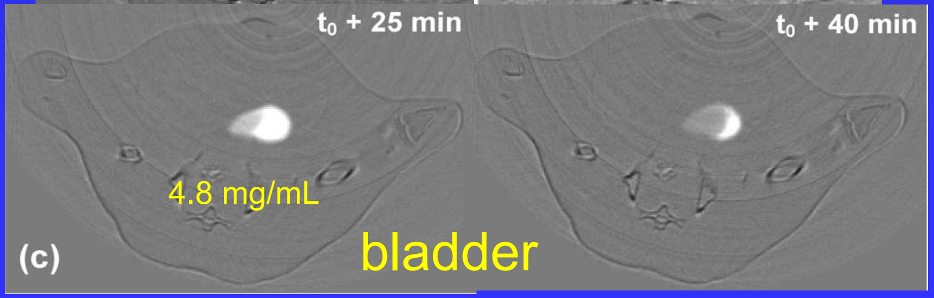
Gd and Au n-particles for imaging and therapy

- N-particles: very interesting contrast agent (longer vascular half-life than molecular contrast agents) → can be monitored for a longer time.
- Au: biocompatible. Gd chelate coated gold n-particles: sensitive to MRI and CT and adapted for therapy as dose enhancer
- CT with monochromatic X-rays: quantitative evaluation at spatial high resolution



free circulation in the rat blood vessels without undesirable accumulation in the lungs, spleen, liver

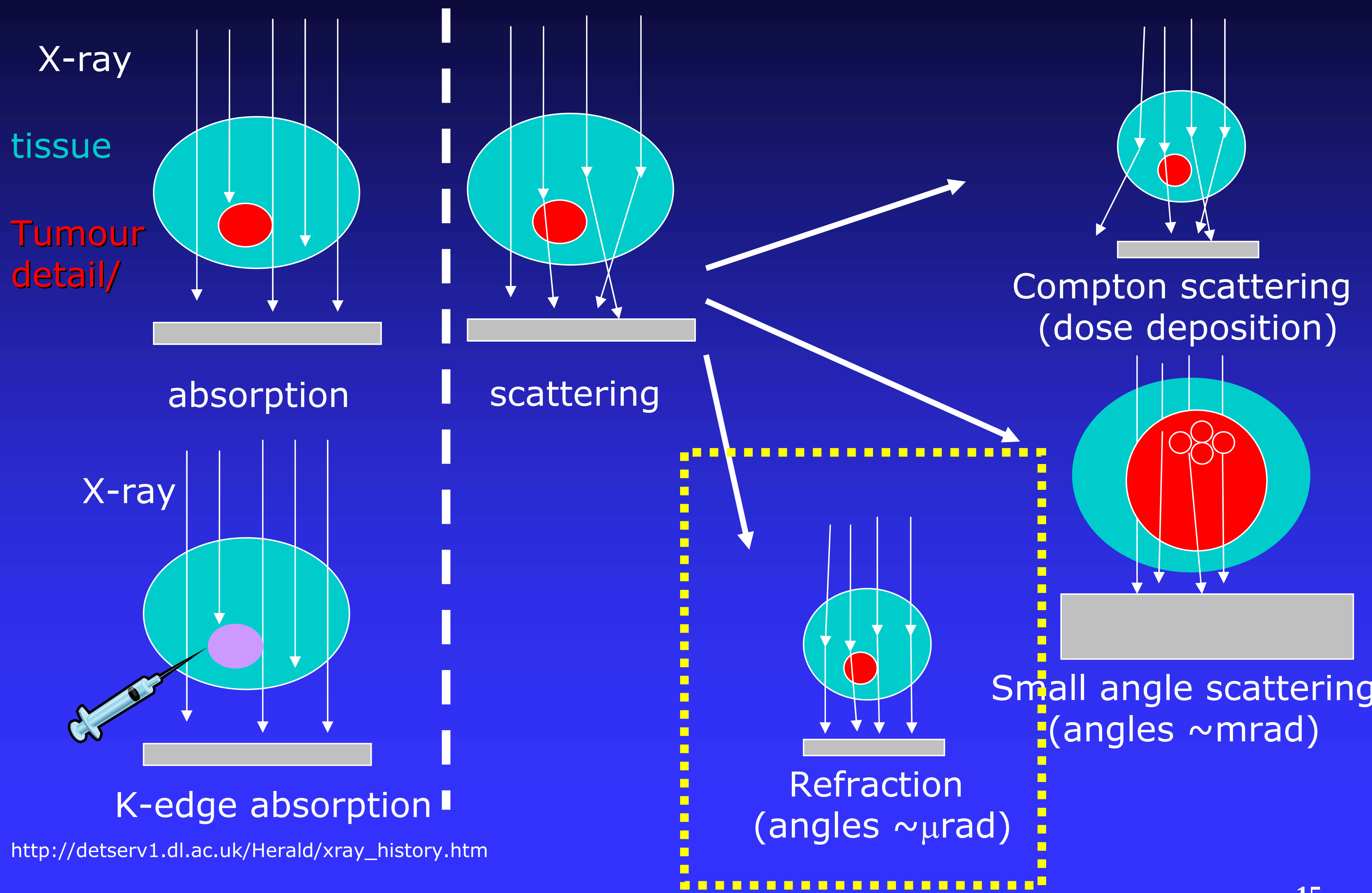




Gold K-edge subtraction Imaging (80.7 keV)

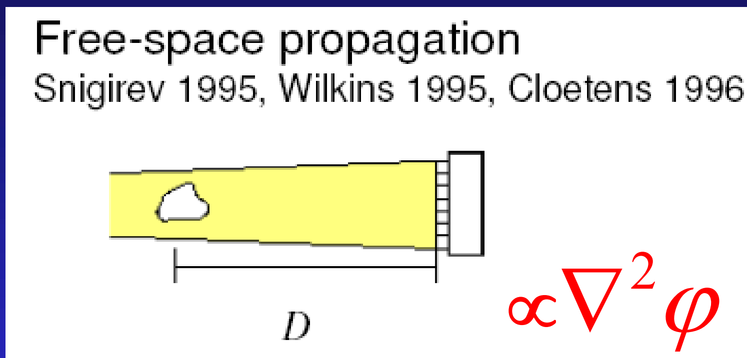
C. Alrich et al. J. Am. Chem. Soc. 2008, 130, 5908

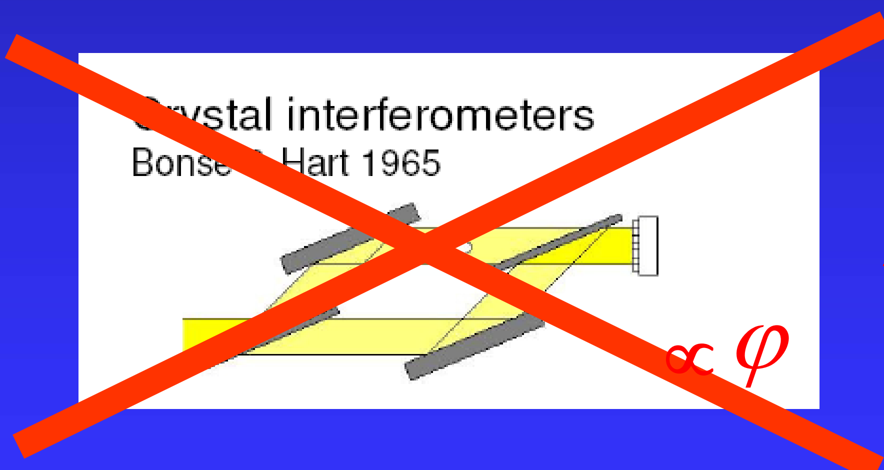
Interaction of X-rays with tissues (pictorial)

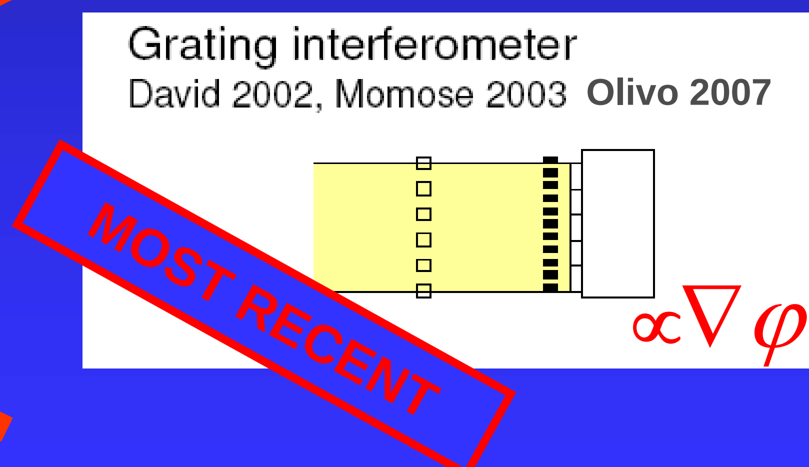


http://detserv1.dl.ac.uk/Herald/xray_history.htm

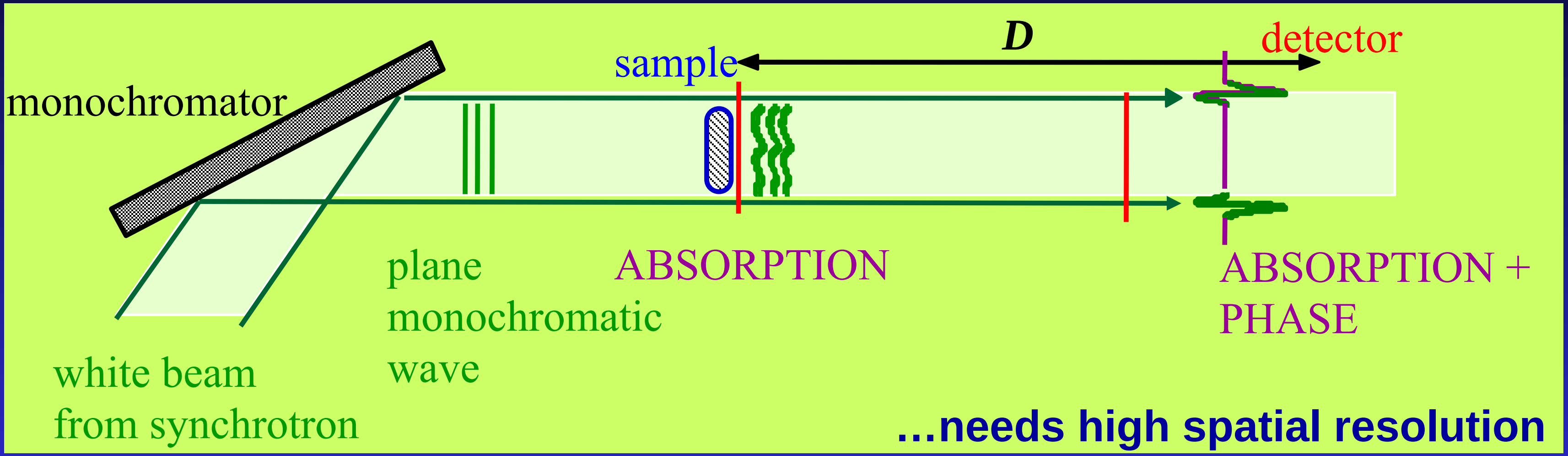
Phase contrast imaging techniques





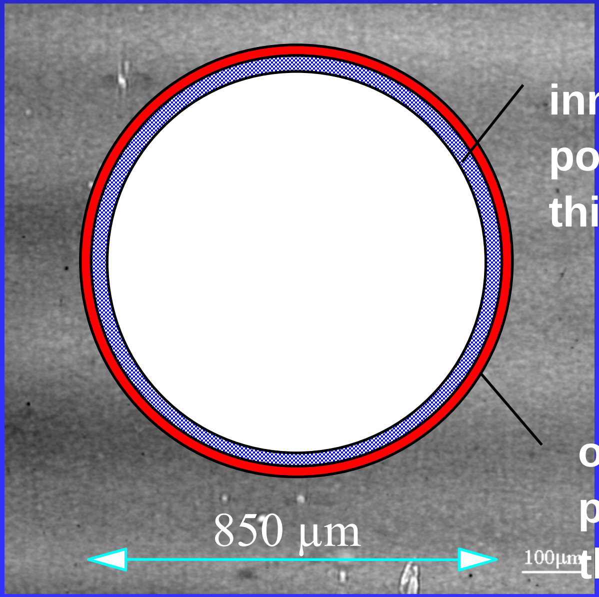


Propagation-based imaging



Absorption

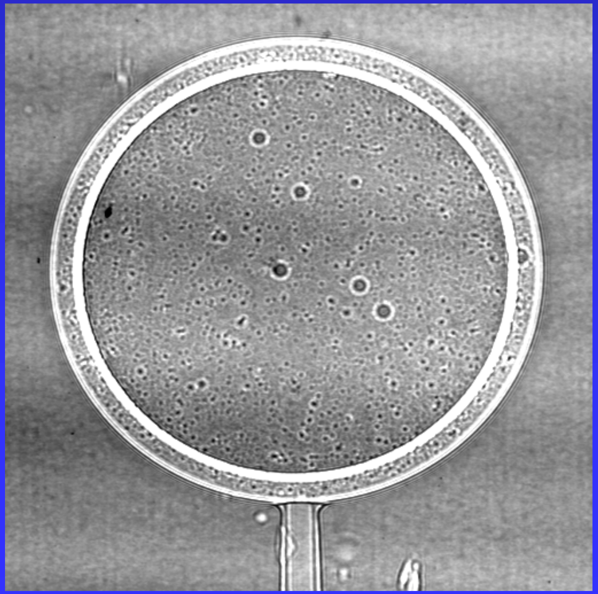
Polymer sphere with two layers



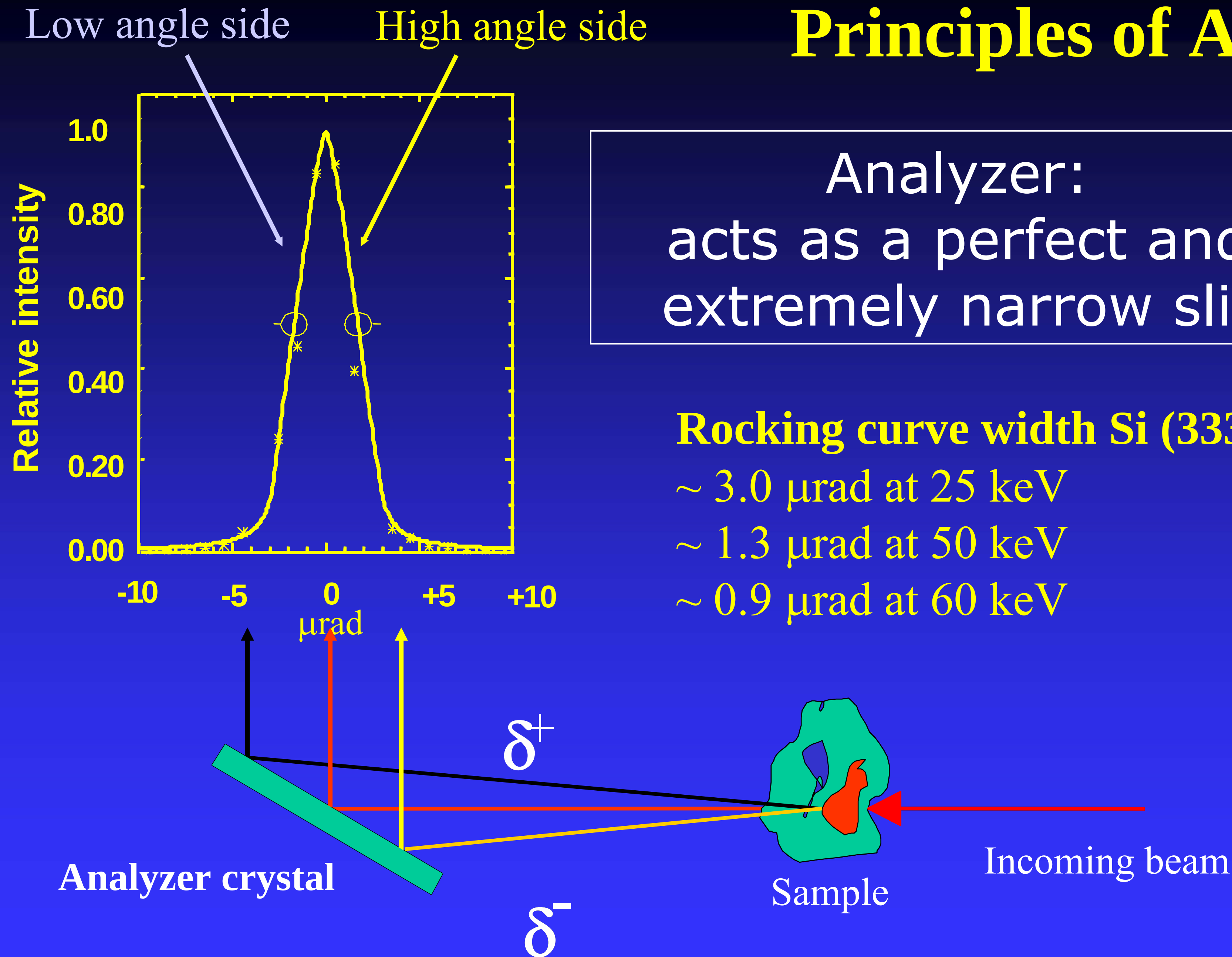
inner layer
polystyrene
thickness 30 µm

outer layer
parylene
thickness 15 µm

Propagation



Principles of ABI



Analyzer:
acts as a perfect and extremely narrow slit

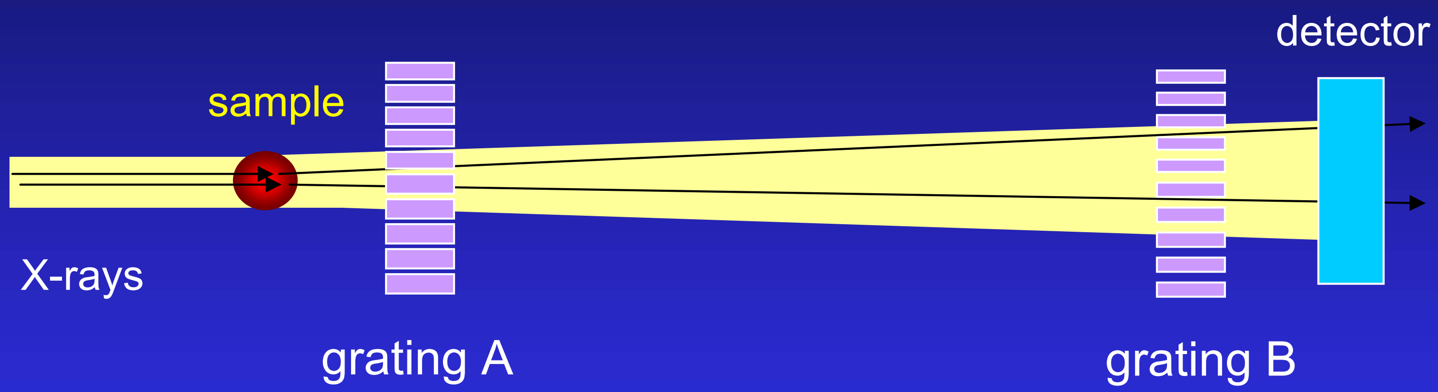
Rocking curve width Si (333)

~ 3.0 µrad at 25 keV

~ 1.3 µrad at 50 keV

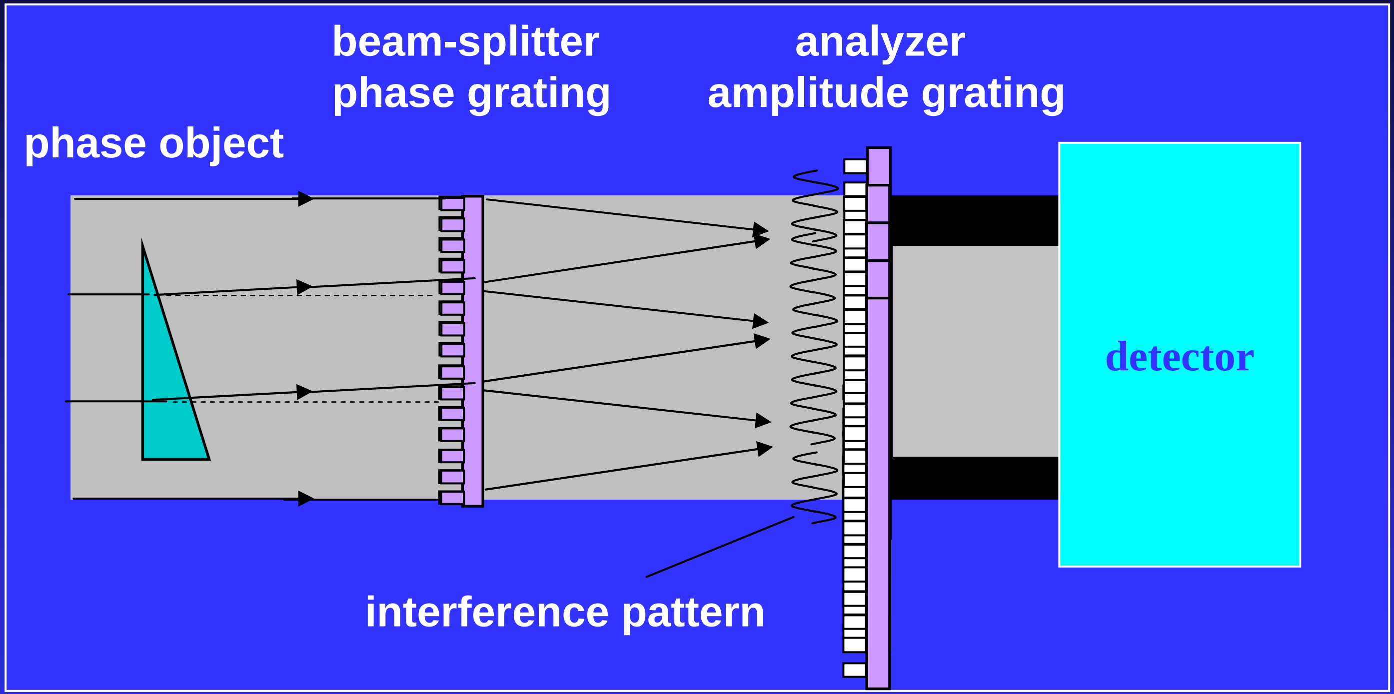
~ 0.9 µrad at 60 keV

Phase contrast Imaging Techniques



Grating interferometer technique

Grating interferometer



Scan one grating ("phase stepping")

→ Yields absorption image and phase-gradient image

F. Pfeiffer, C. David, T. Weitkamp et al. Nature Physics 2007

PhC Mammography

- Free Propagation: clinical trials at ELETTRA (L. Rigon’s talk)

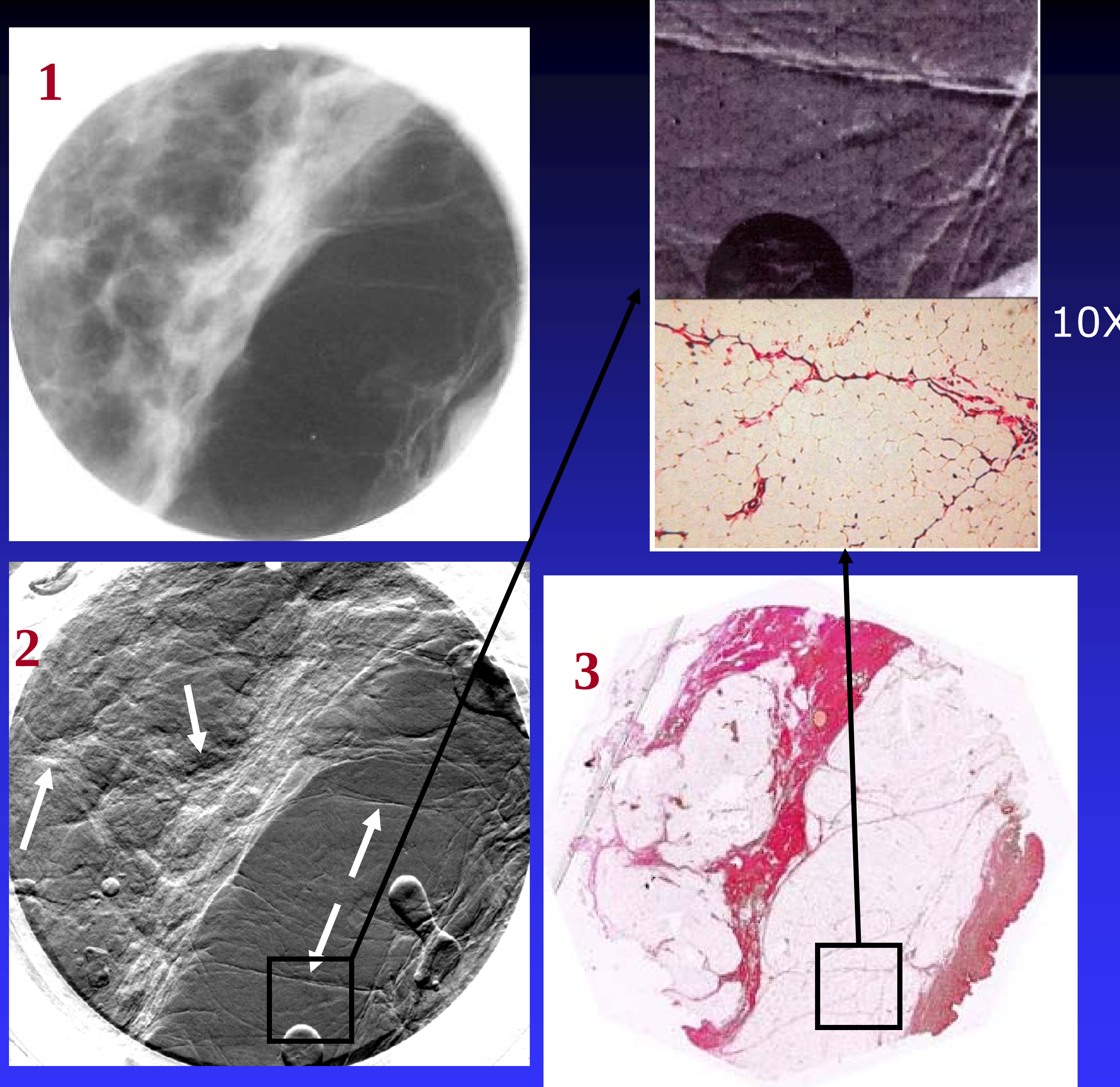
Analyzer Based Imaging Mammography: latest results

Carcinoma Medullare

- 1 Siemens Mammomat 3000 -23 kVp- 5.6 mAs; MGD=0.4 mGy

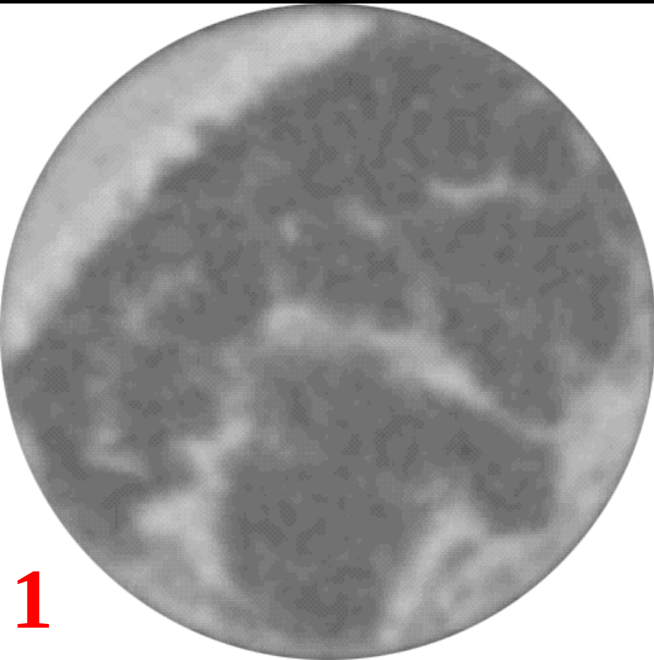
- 2 ABI 25 keV minus 0.7 µrad. Si(333); MGD= 0.6 mGy

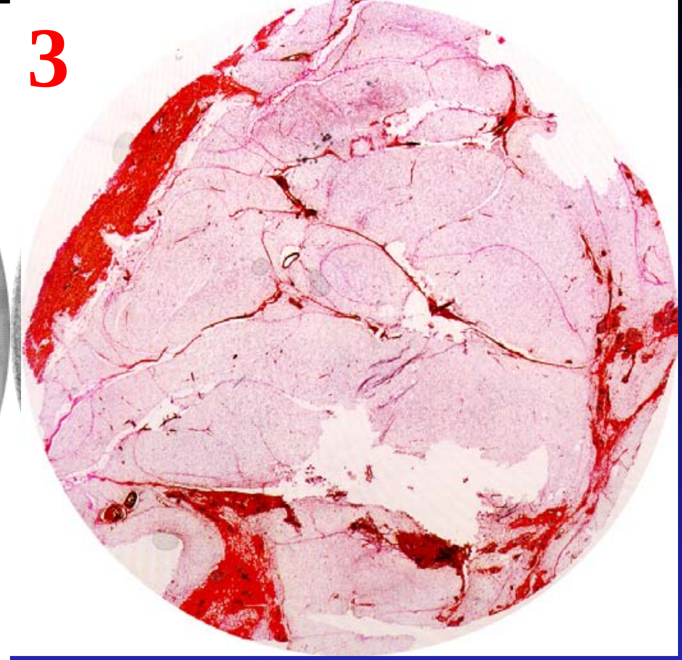
- 3 Histology



Keyriläinen et al. European Journal of Radiology 53, 226-237 (2005)

Carcinoma

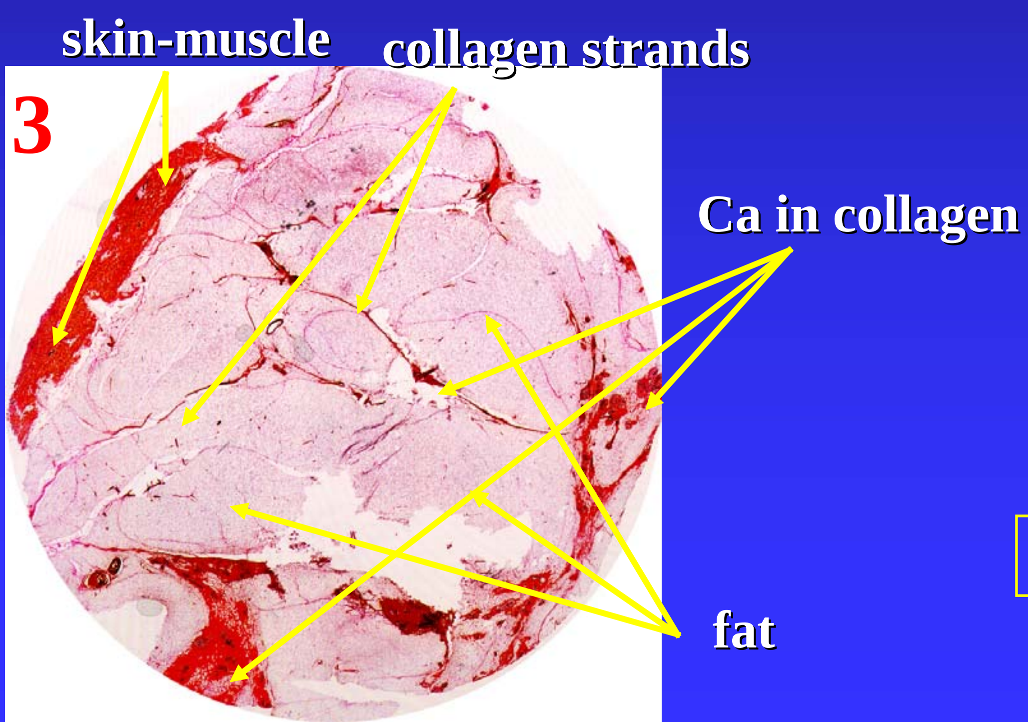




- 1 Toshiba Asteion TSX - 021A CT-scanner (80 kVp)

- 2 ABI 33 keV- 0 µrad

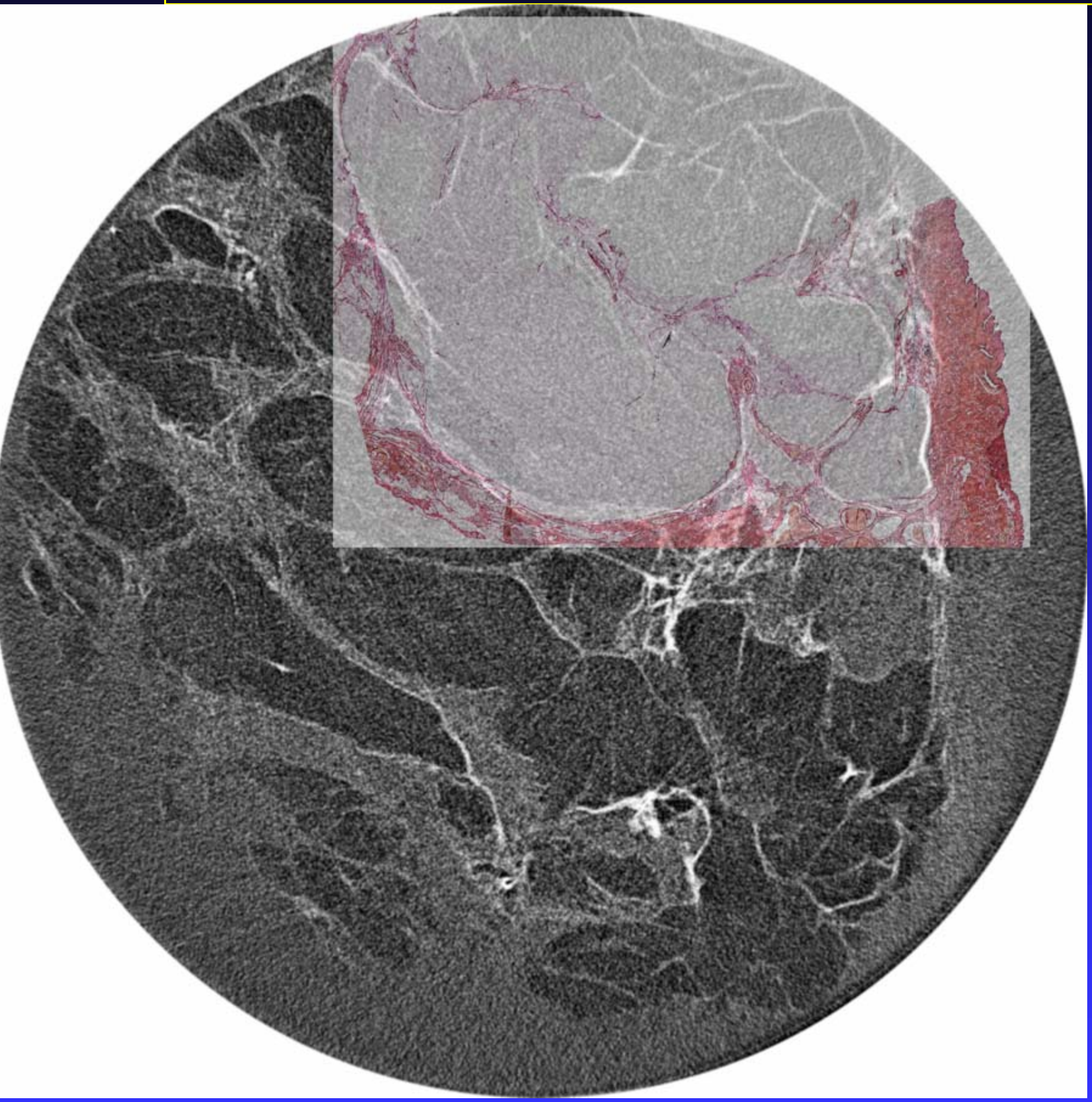
- 3 Histology



CT-ABI

Bravin et al. Phys.Med. Biol. 2007

Lobular Breast carcinoma-CT



Top

Si(333)

33 keV

720 projections

Voxel: 50^3 μm^3

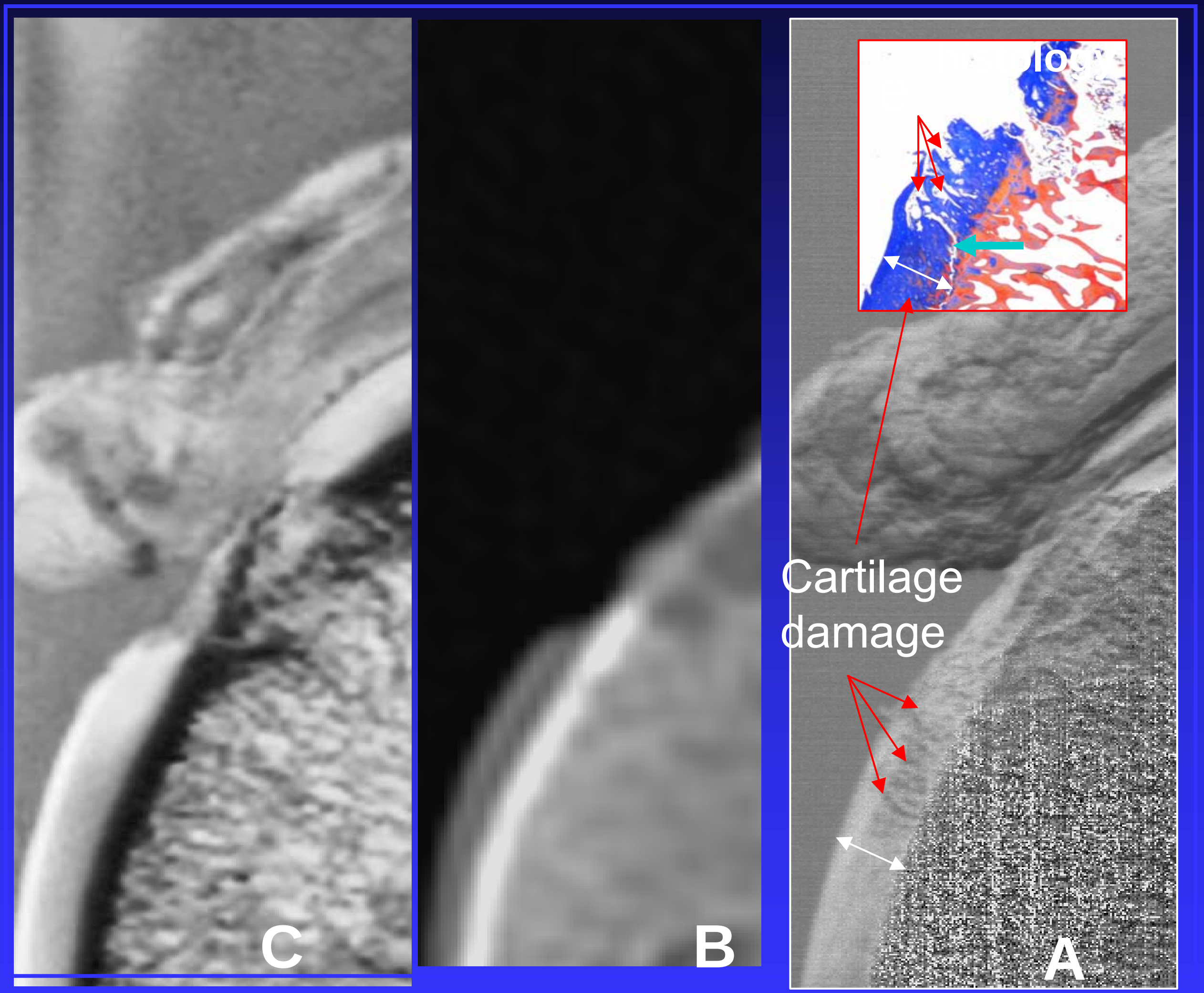
1.9 mGy

J. Keyriläinen et al. Radiology 2008; 249: 321-327 (October)

Articular cartilage imaging

- Free propagation on cartilage: P. Coan’s talk

HIP - ABI vs conventional techniques



MRI　**Conventional CT**　**ABI** (Refraction Im.)

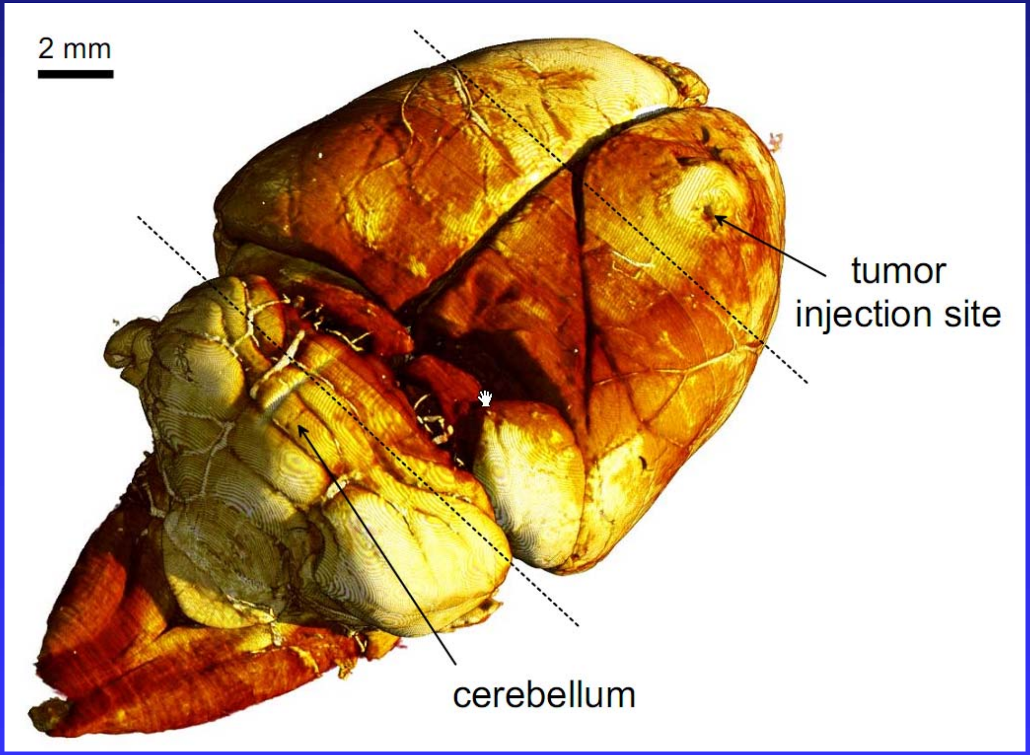
Despite A is a projection image structural damage of cartilage is displayed that is invisible in MRI and CT

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)

Gratings based imaging

Exploiting conventional sources: Grating imaging

Extended (low spatially coherent) sources can be used for PhC imaging!



E=24.9 keV
FoV=16x16 mm^2
Pixel size 15.7x15.7 μm^2

F. Pfeiffer, et al. Phys. Med. Biol. (2007) 6923

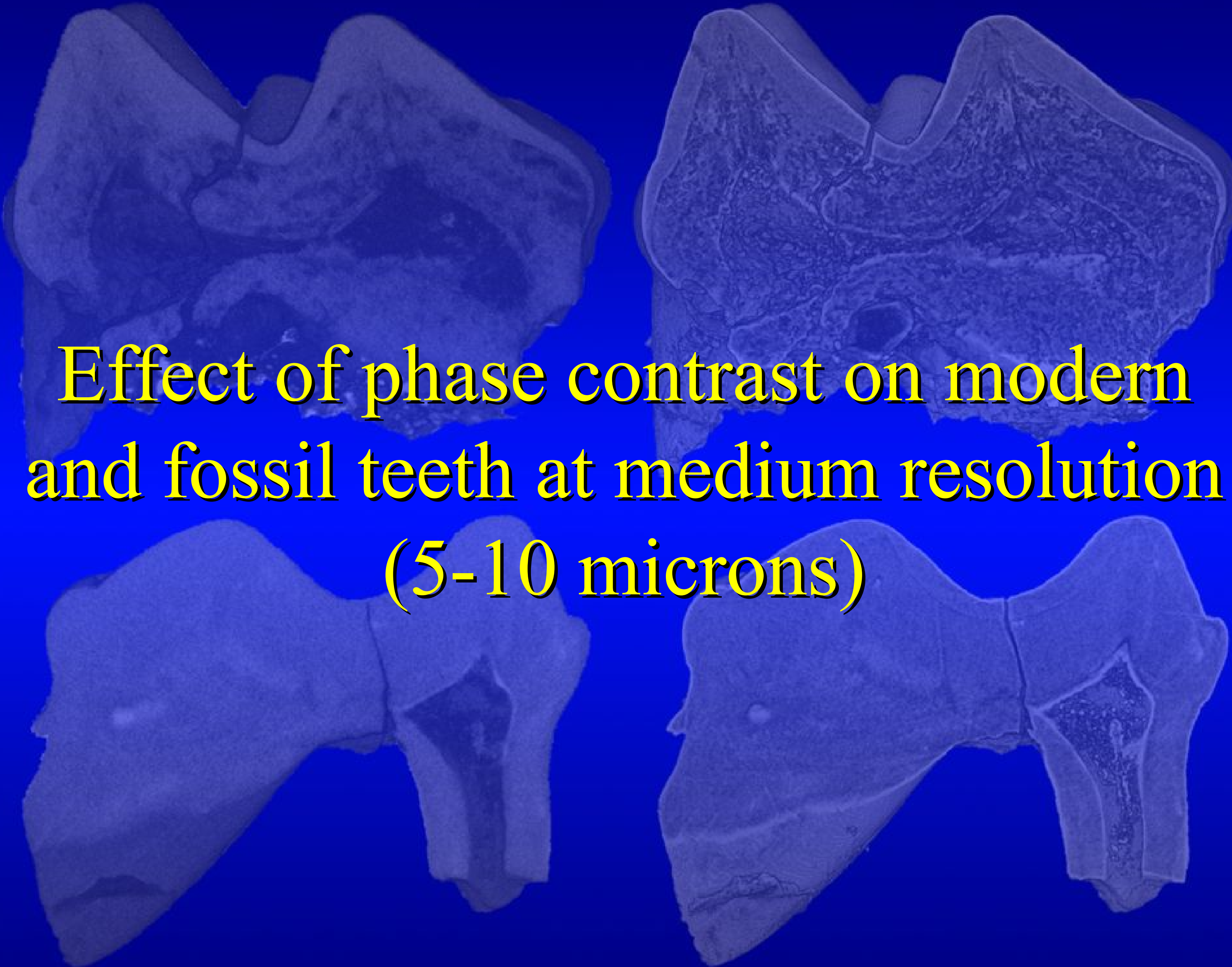
Imaging

Biomedical imaging

Paleontology

Cultural heritage

Effect of phase contrast on modern and fossil teeth at medium resolution (5-10 microns)



- Enamel microstructural features can bring a lot of information about diet, phylogeny, development and life history.
- Most of the existing techniques are destructive or are not able to investigate microstructure on complete teeth.

Imaging

Biomedical imaging

Paleontology

Cultural heritage

Examples studied at ID21 (ESRF) since 3 years – looking backwards

Glasses decoration

"Polychrome Etruscan glass: first non-destructive characterisation with synchrotron µXRF, µXANES and XRPD", **R. Arletti, et al., *Applied Physics A*, in press.**

Bones

"Synchrotron radiation and cultural heritage: combined XANES/XRF study at Mn K-edge of blue, grey or black coloured palaeontological and archaeological bone material", **I. Reiche & E. Chalmin, *J. Anal. At. Spectrom.*, <u>23</u>, 799 - 806 (2008).**

Varnishes on musical instruments

"Insights into the varnishes of historical musical instruments using synchrotron micro-analytical methods", **J.-P. Echard, et al., *Applied Physics A*, <u>92</u>, 77-81 (2008).**

Paintings

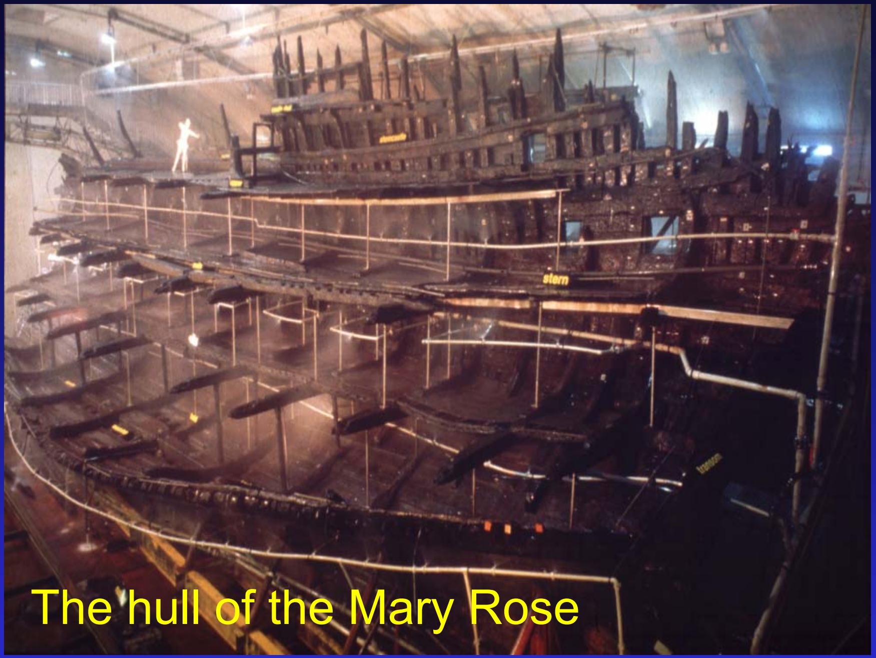
"Discovery of unusual minerals in Paleolithic black pigments from Lascaux (France) and Ekain (Spain)", E. Chalmin et al., *SLAC-PUB-12224* (2006).

"Archaeological applications of XAFS: prehistorical paintings and medieval glasses", **F. Farges, et al., *Phys. Scr.*, <u>T115</u>, 885-887 (2005).**

"Synchrotron-based X-ray spectro-microscopy used for the study of an atypical micrometric pigment in 16th Century paintings", **M. Cotte et al., *Anal. Chem.*, <u>79</u>, 6988-6994 (2007).**

"Applications of synchrotron-based micro-imaging techniques to the chemical analysis of ancient paintings", **M. Cotte, et al., *J. Anal. At. Spectrom.*, <u>23</u>, 820-828 (2008).**

Marine-archaeological wood conservation



The hull of the Mary Rose

The Mary Rose was built in Portsmouth in 1511 and served as English King Henry VIII's main warship until she sank in 1545 during an engagement with the French fleet.

The ship lay buried in the seabed off the South coast of England until she was rediscovered in 1971, salvaged in 1982. She is currently undergoing conservation process.

- *Vasa* (Sweden, sunk in 1628)
- *Mary Rose* (U.K,1545)
- *Batavia* (Western Australia, 1629)

Wooden shipwrecks
preserved in seawater

↓

accumulation of reduced sulfur compounds
0.5 – 2 mass% (several tons)

Fe ↓ **O_2**

in the moist wood
$S \rightarrow H_2SO_4$

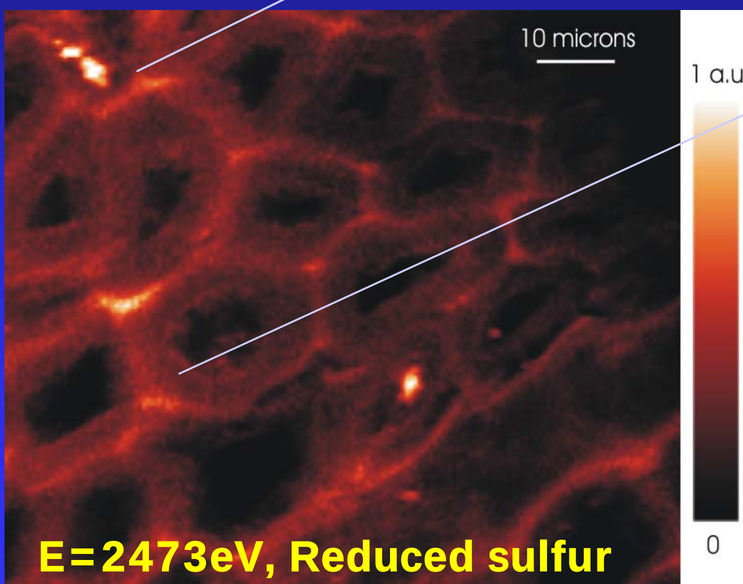
↓

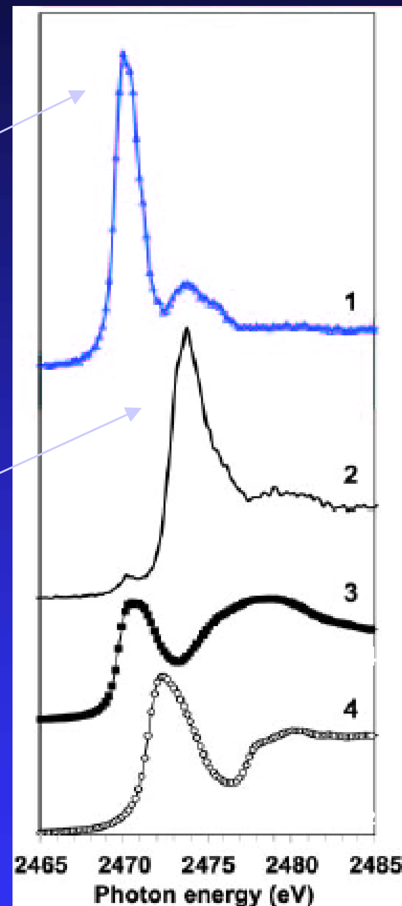
acid hydrolysis of the cellulose fibers

M. Sandström et al., Nature, 415 (2002)

Sulfur accumulation in the timbers of the Mary Rose

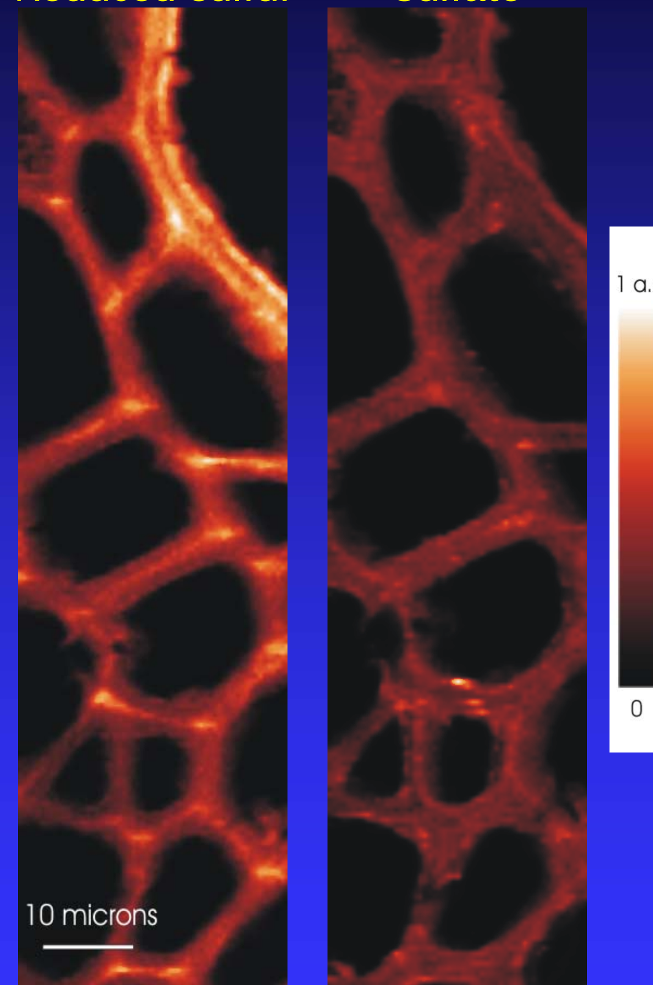
- Scanning X-ray Microscopy images of sulfur in wood slices from Mary Rose timbers.
- Wood under spray treatment





E=2473eV
Reduced sulfur

E=2482eV
Sulfate



Thiols in
lignin-rich cell lamella

M. Sandström et al., PNAS 102 (40) (2005)

Examples studied at ID21 (ESRF) since 3 years – looking forward

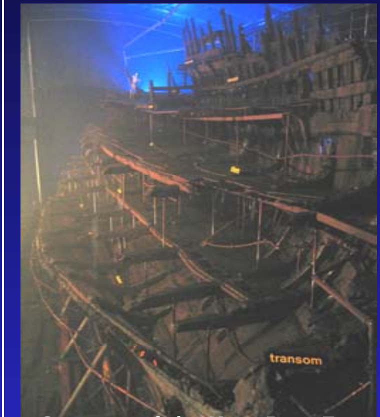
Corrosion in ancient nails

"Buried iron archaeological artefacts: Corrosion mechanisms related to the presence of Cl-containing phases", **S. Réguer, et al., Corrosion Science, 49, 2726-2744 (2007).**

"Local and structural characterisation of chlorinated phases formed on ferrous archaeological artefacts by µXRD and µXANES", **S. Réguer, et al., NIMB, 240, 500-504 (2005).**

"Corrosion of iron archaeological artefacts in soil: characterisation of the corrosion system", **D. Neff, et al., *Corrosion Science*, 47, 515-535, (2005).**

Wreck of warship



Courtesy of the Mary Rose Trust

"Sulfur accumulation in the timbers of King Henry VIII's warship Mary Rose: A pathway in the sulfur cycle of conservation concern", **M. Sandström et al., PNAS, 102, 14165-14170 (2005).**

"Sulfur and iron speciation in recently recovered timbers of the Mary Rose revealed via X-ray absorption spectroscopy", **K.M. Wetheralla et al., *Journal of Archaeological Science*, 35, 1317-1328 (2008).**

Painting alterations

"Blackening of Pompeian Cinnabar paintings studied by X-ray micro-spectroscopic imaging", **M. Cotte, et al., *Anal. Chem.*, 78, 7484-7492 (2006).**

"Applications of synchrotron-based micro-imaging techniques to the chemical analysis of ancient paintings", **M. Cotte, et al., *J. Anal. At. Spectrom.*, 23, 820-828 (2008).**

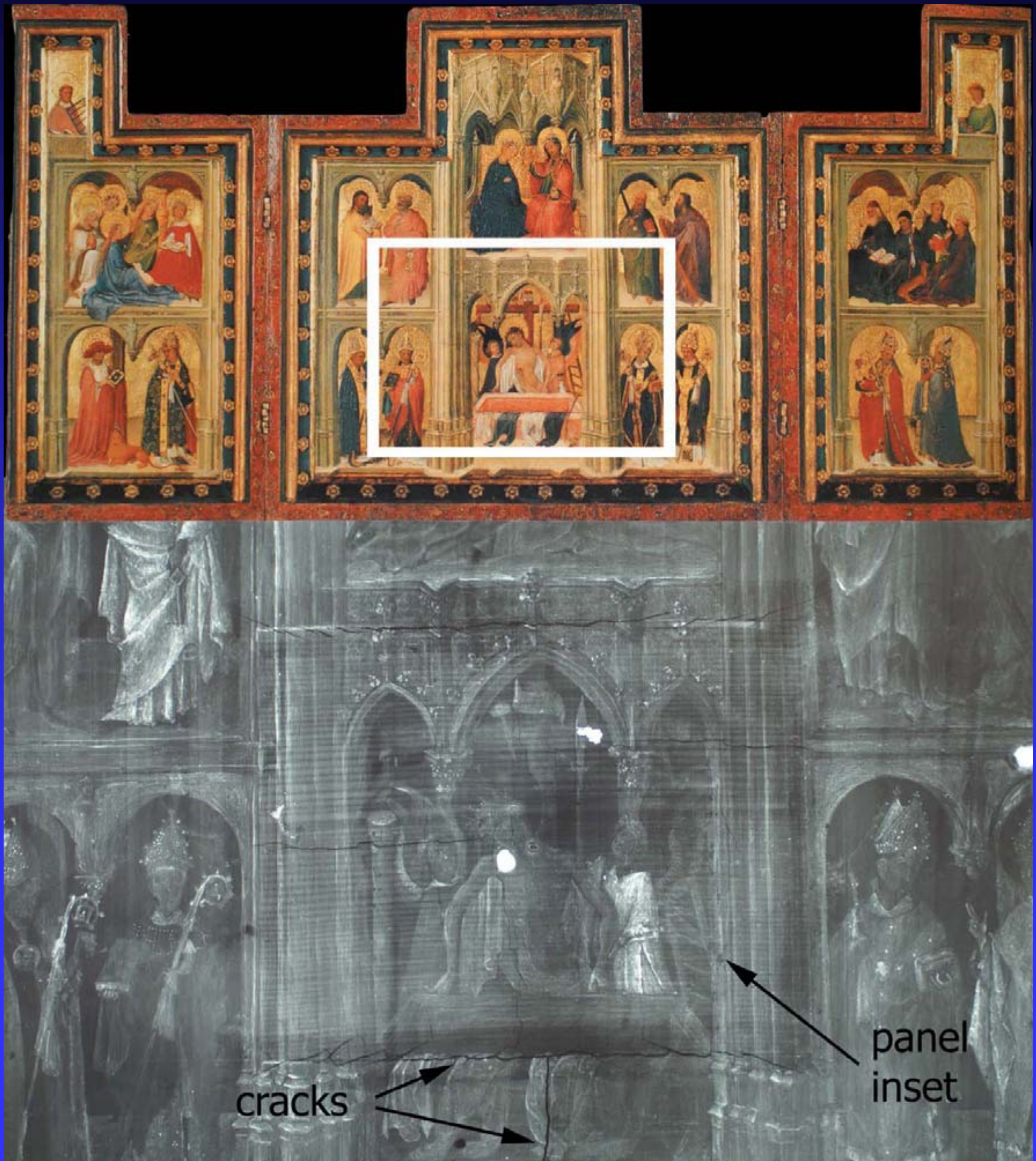
"Micro-analytical study of interactions between oil and lead compounds in paintings", **M. Cotte, et al., *Applied Physics A*, 89 (4), 841-848 (2007).**

"Weathering of gilding decorations investigated by SR: development and distribution of calcium oxalates in the case of Sant Benet de Bages (Barcelona, Spain)", **A. Lluveras, et al., *Applied Physics A*, 90, 23-33 (2008).**

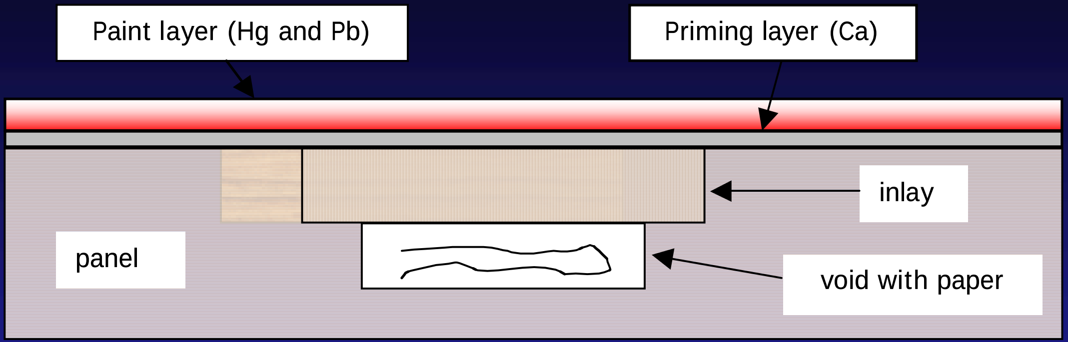
“Inside” paintings

Norfolk Triptych-

The Netherlands’ oldest painting

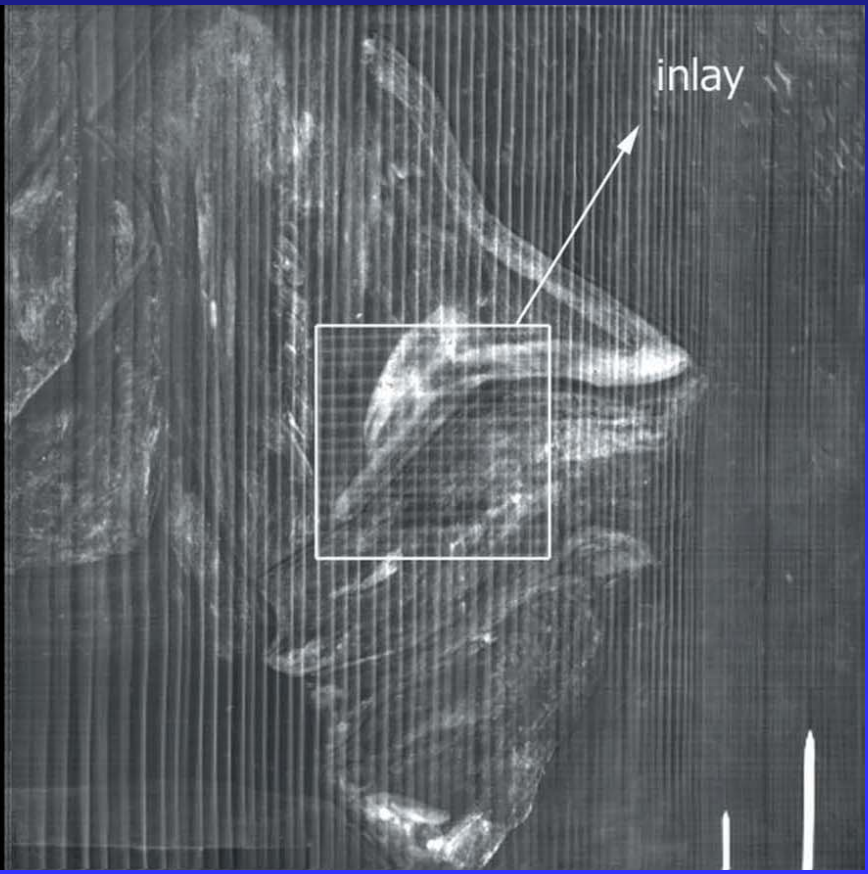


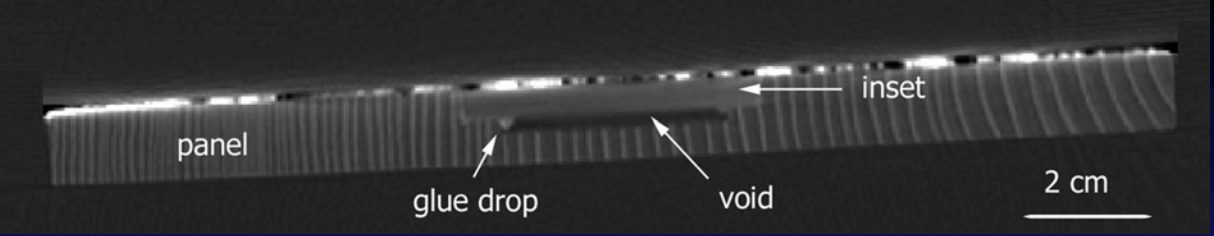
“Inside” paintings



Visible light picture

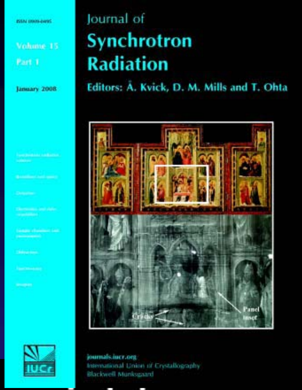
Phase contrast ABI imaging 35 keV

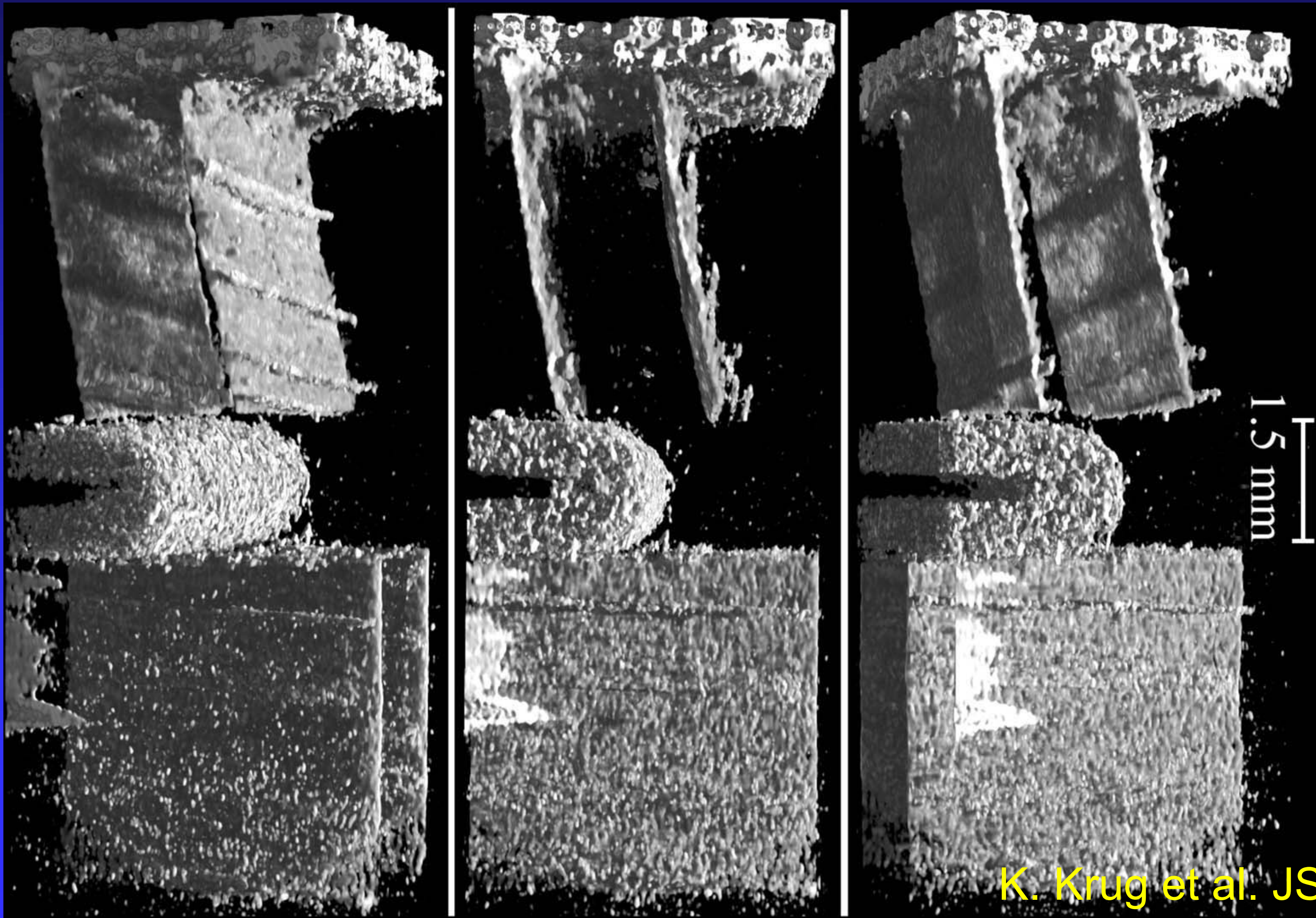




Absorption CT image of the panel.

Laminography





paint layers
priming layer

wood grain
of inlay

fold in paper

wood grain
of panel
(perpendicular
to inlay)

K. Krug et al. JSR 15, 2008

Radiotherapy:

Preclinical experience and clinical perspectives

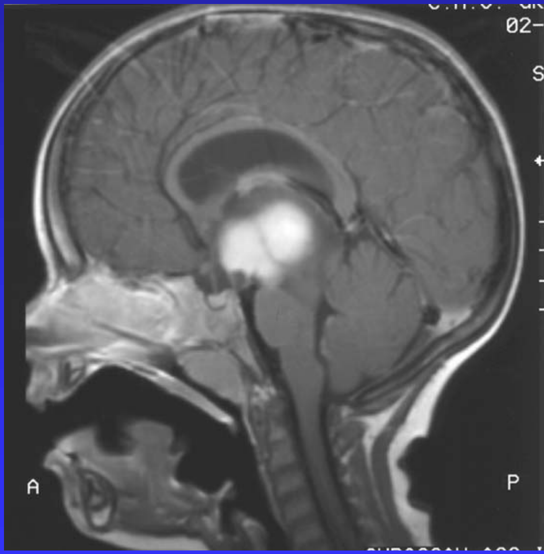
Cerebral Tumors

- Epidemiology : 3000 cases/year in France
- 65 % are glioma (high grade tumors)
- Morbidity: short life expectancy (2-36 months)

Cancer of the nervous system is the second most common form of cancer for children, after leukemia

Radiotherapy is only palliative for various tumor grades and locations

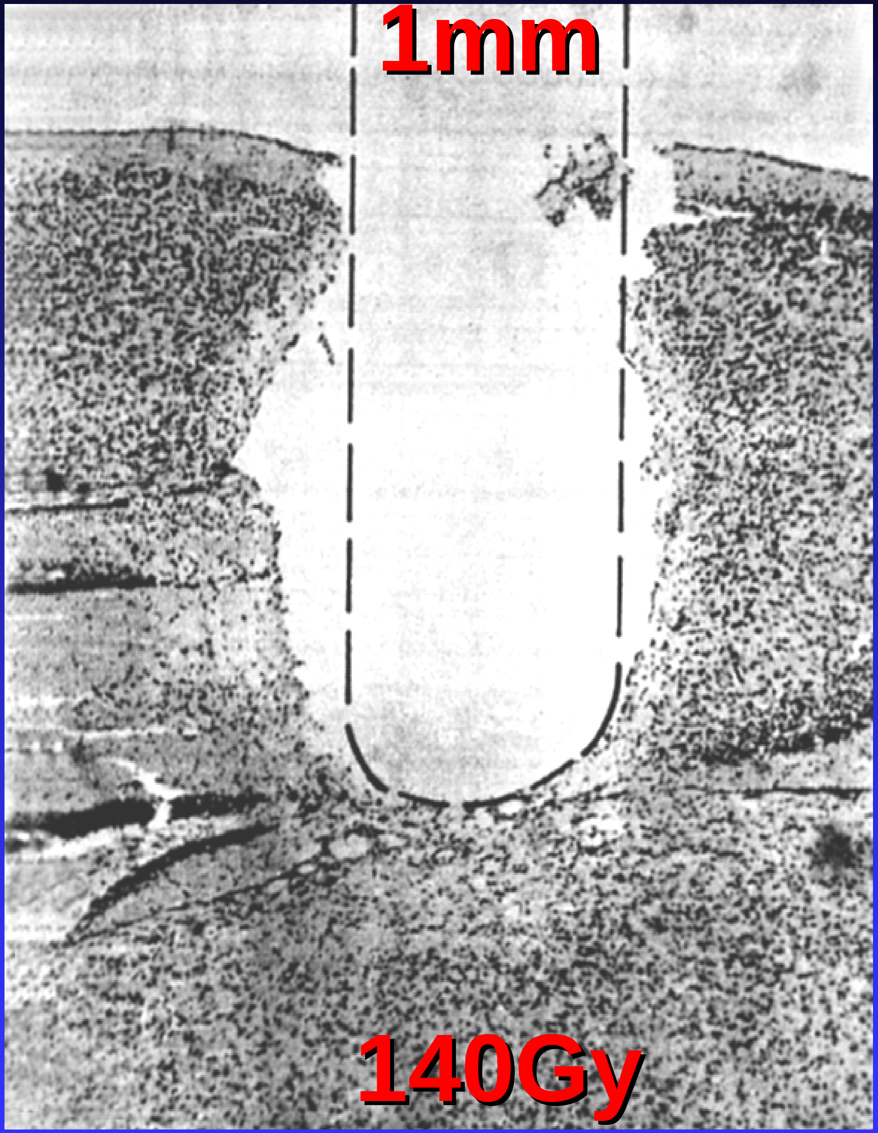
- IMRT-Radiotherapy
- 50 Gy at the tumor location
- 25 fractions @ 5/week
- ***Limited by tissue tolerance***

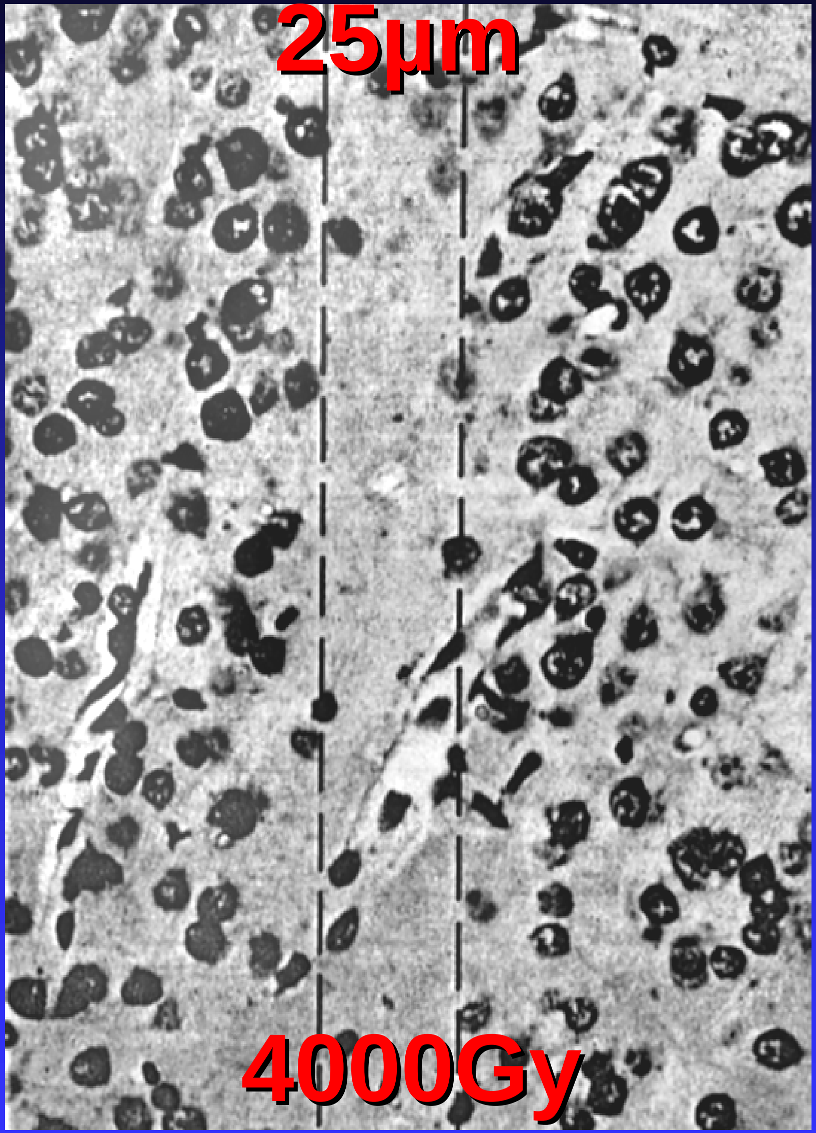


Is there another way for increasing the dose delivered to the tumour while sparing the surrounding tissues ?

Microbeam Radiation Therapy (MRT)

MOUSE BRAIN, VISUAL CORTEX





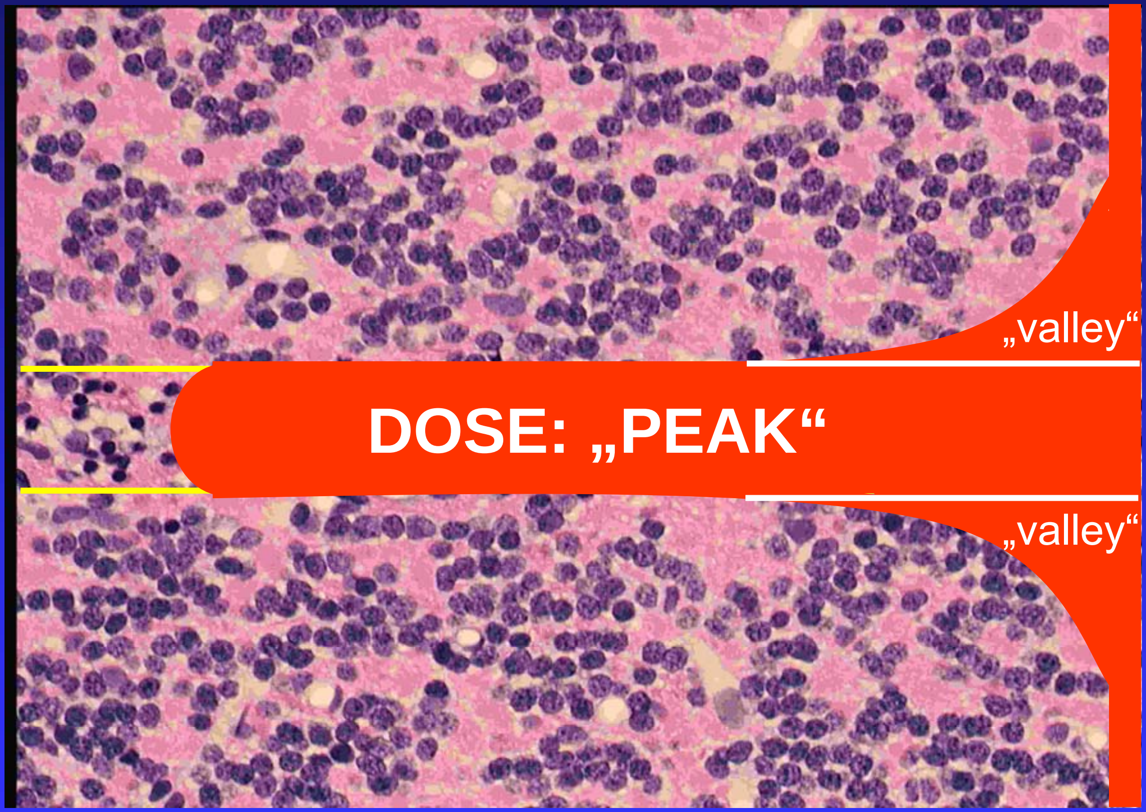
Zeman et al, Radiat Res 15, 496,1961

Rat cerebellum after MRT irradiation

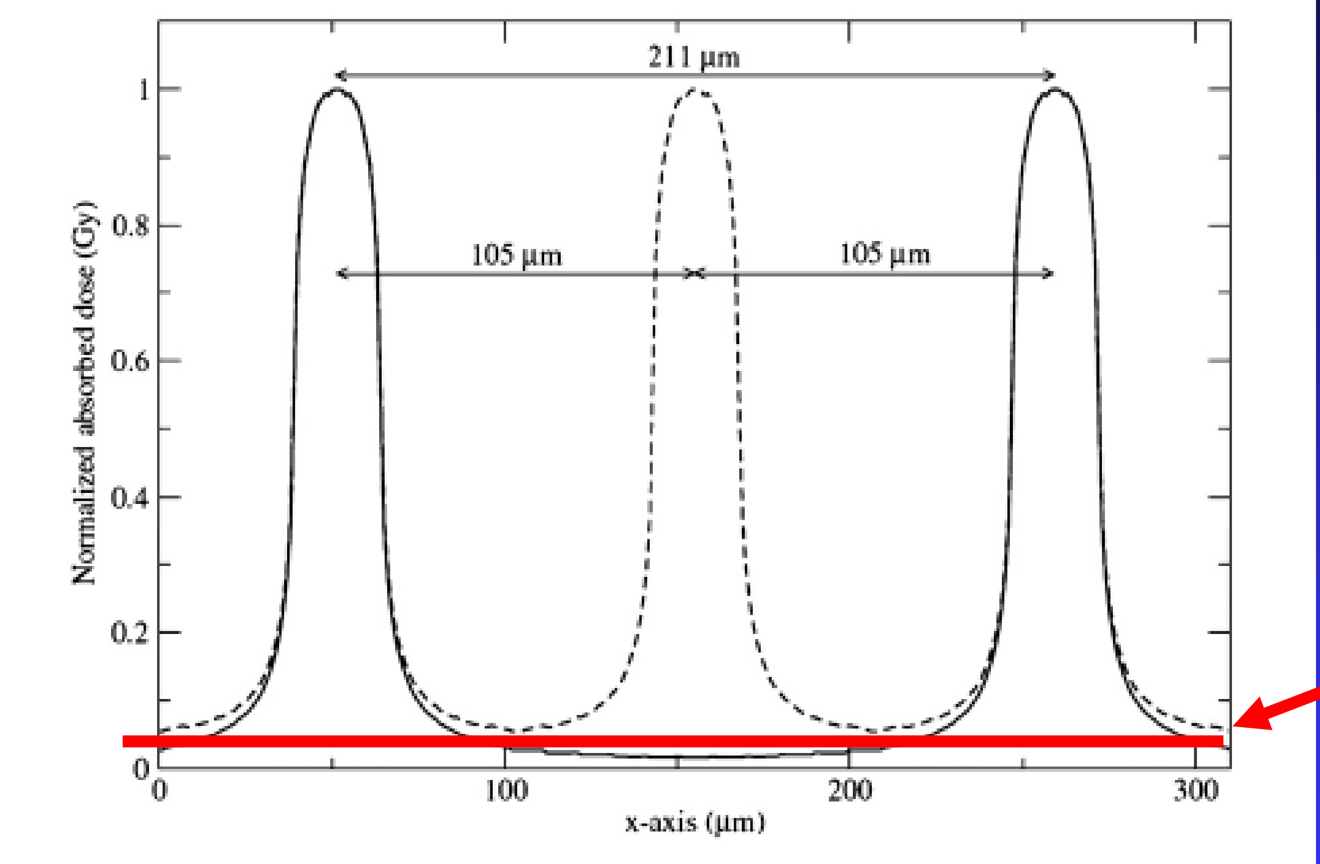
Entrance dose:
2000 Gy

25 µm-wide microplane

12 h after irradiation



The importance of Peak to Valley Dose Ratios (PVDRs)



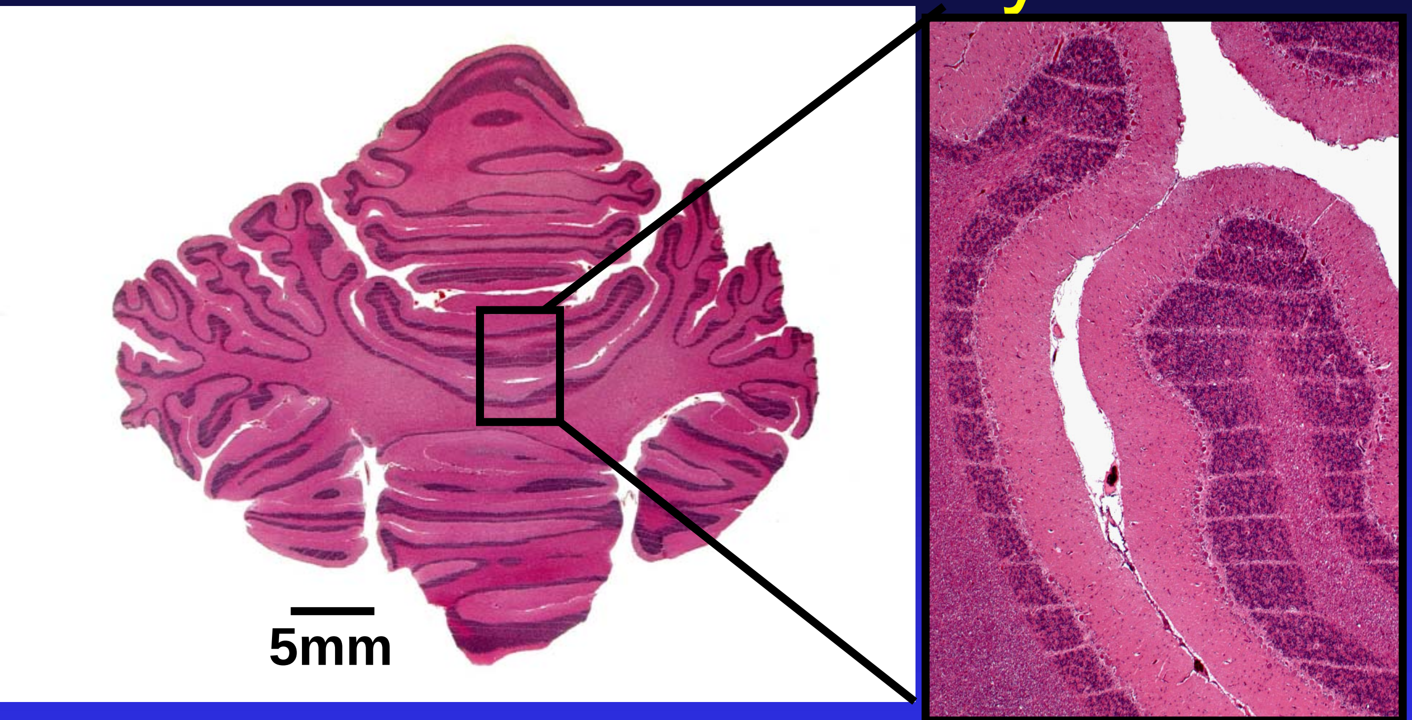
Tissue tolerance threshold dose for healthy tissue homogeneous irradiation

The dose in the valleys that creates a dose offset in the tissues, has to be below the tolerance threshold dose

Microbeam Radiation Therapy:

Tissue sparing effect

Piglet irradiation (cerebellum): no secondary effects



Histological section

300 Gy

≈25 µm

200 µm ctc

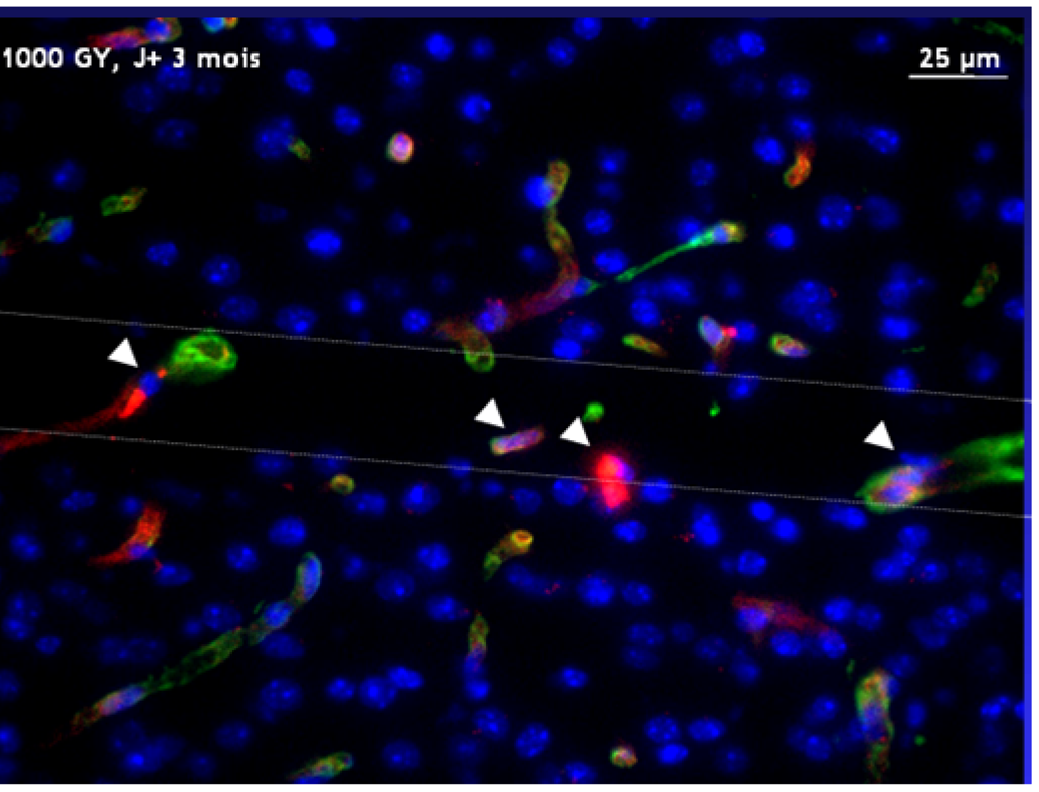
15 months after MRT

No tissue destruction present. Normal appearance of brain and cerebellum tissues irradiated at 300 or 625 Gy.

Animals (20 pigs) were kept alive for ~2 years.

No one animal showed Central Nervous System damage clinical signs

Understanding of phenomenons (intravital biphotonic microscopy and immuno-histo-chemistry)



Collagen Pecam Nuclei

- no alterations of structure of vessel networks in normal brain for 25 microns thickness, until 1000 Gy

- Loss of nuclei along path
- Function of vessel remains adequate normal blood supply (coloured endothelial cells)
- no edema before 1000 Gy

Frozen section of normal mice brain (18 microbeams of 25 microns / 211 microns/1000Gy) , 3 months after MRT.

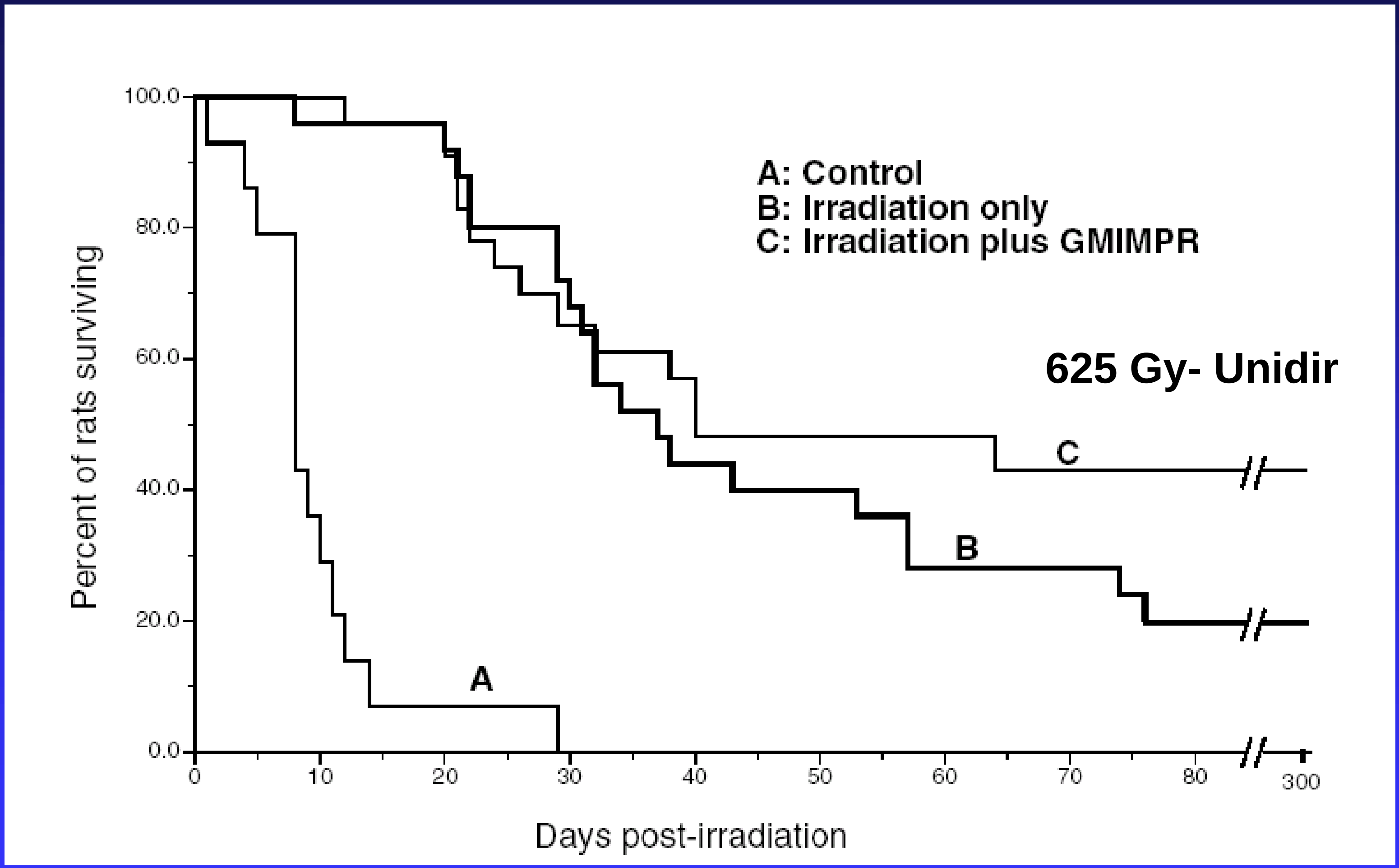
Serduc R, et al. Int J Radiat Oncol Biol Phys. 2006 Apr 1;64(5):1519-27

Microbeam Radiation Therapy:

Curing effect

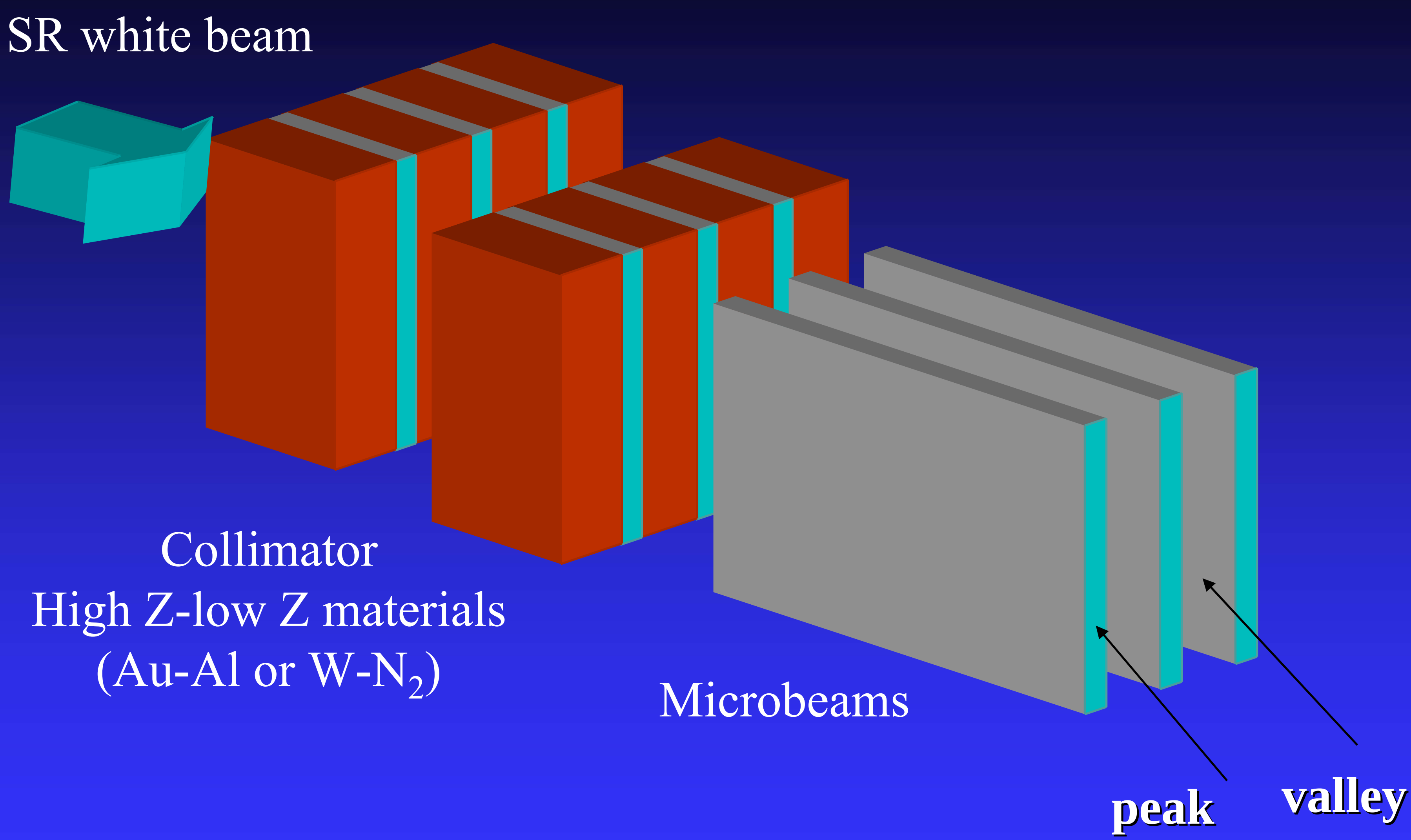
MRT+ Gene-Mediated Immunoprophylaxis

Tumour bearing 9L gliosarcoma rats (MRT treatment at day 14)



H. Smilowitz et al. J. Neurooncology, 78: 135-143, 2006

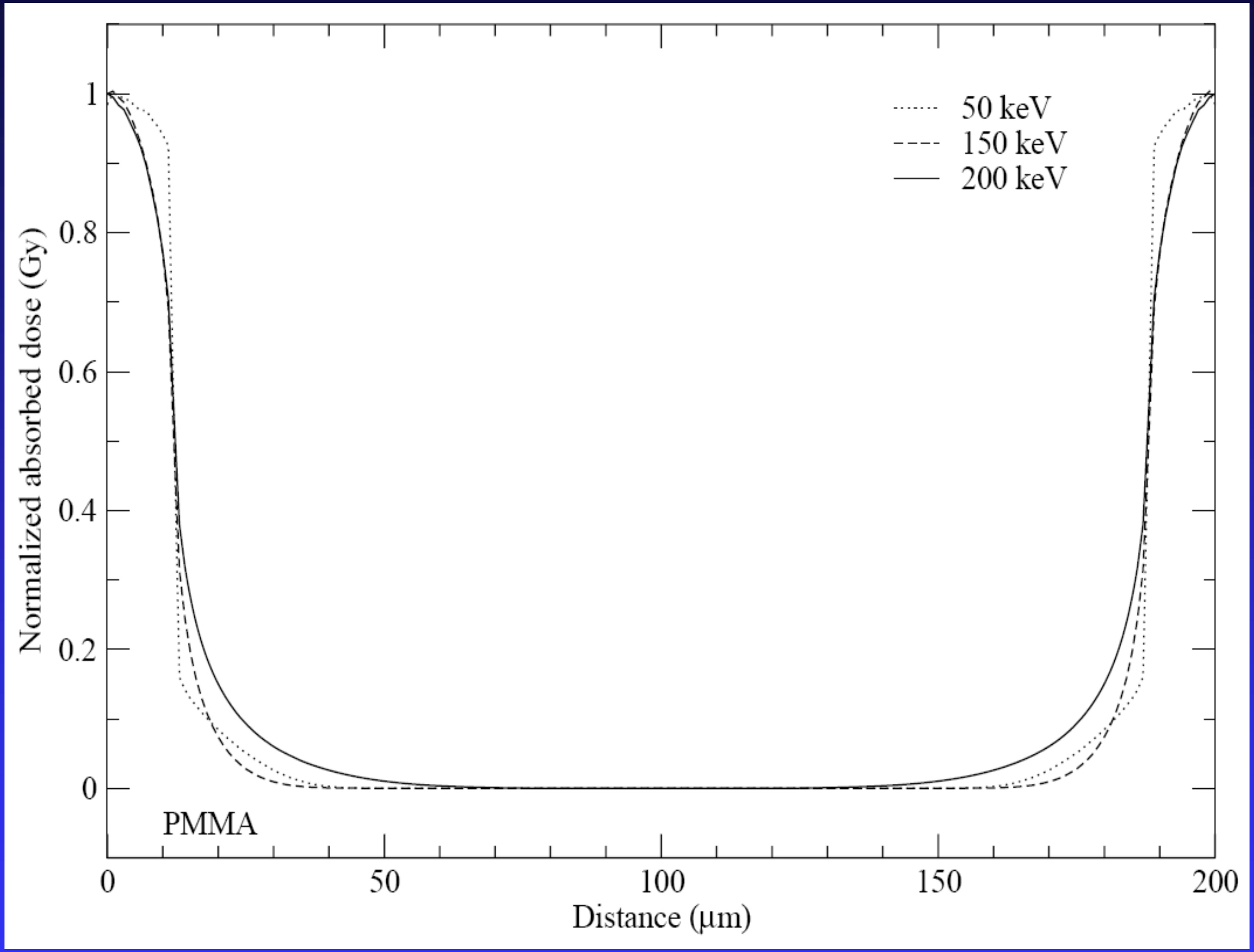
Microbeam production



Microbeam: variable width (0-100 μm), 100-400 μm pitch

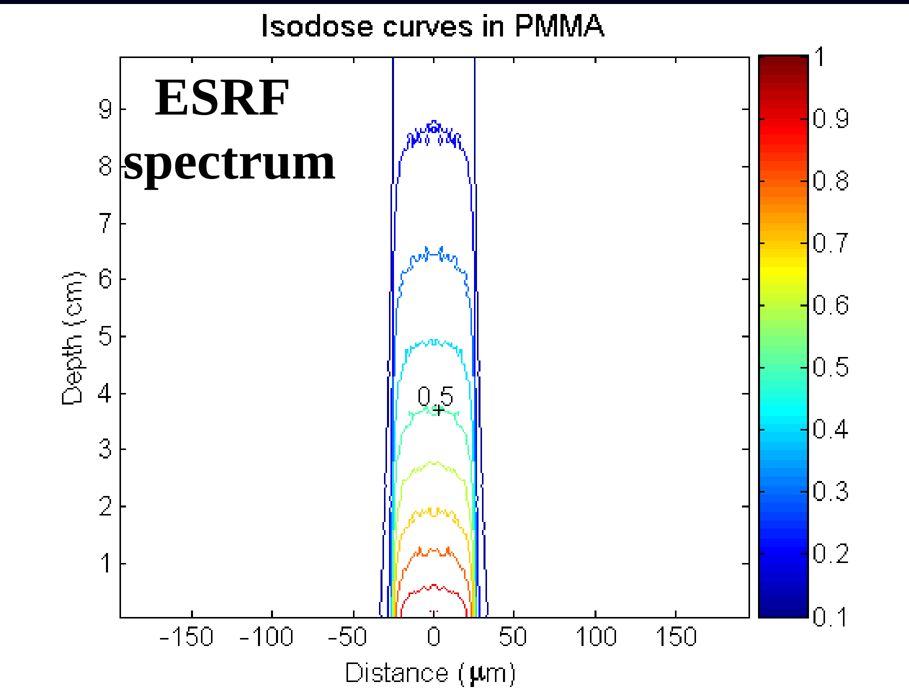
50-125 microbeam array to cover up to 5x5 cm^2

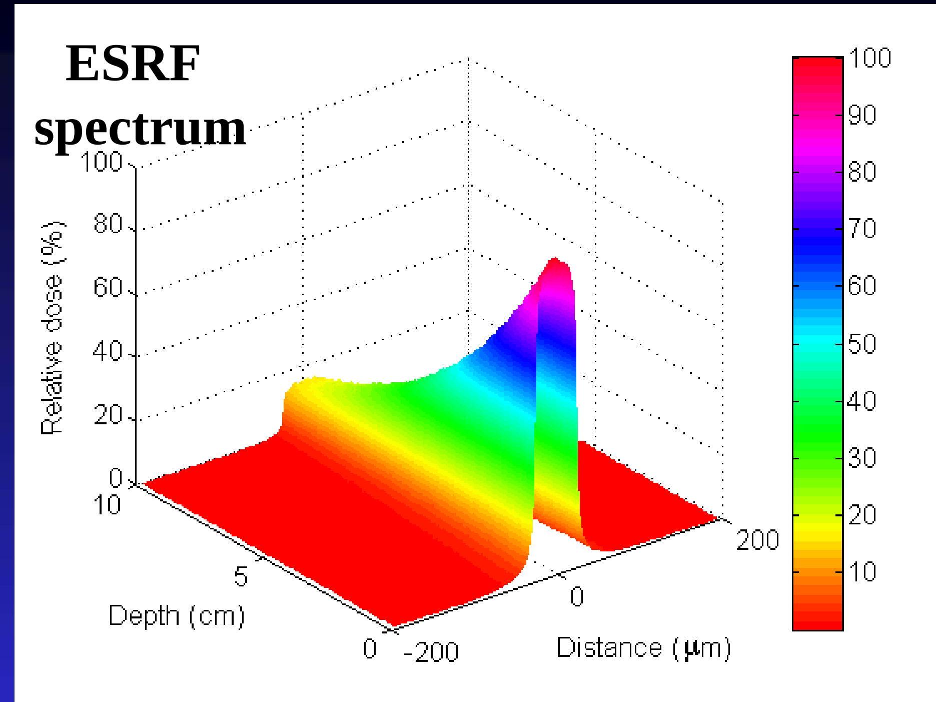
Dose gradient vs. energy

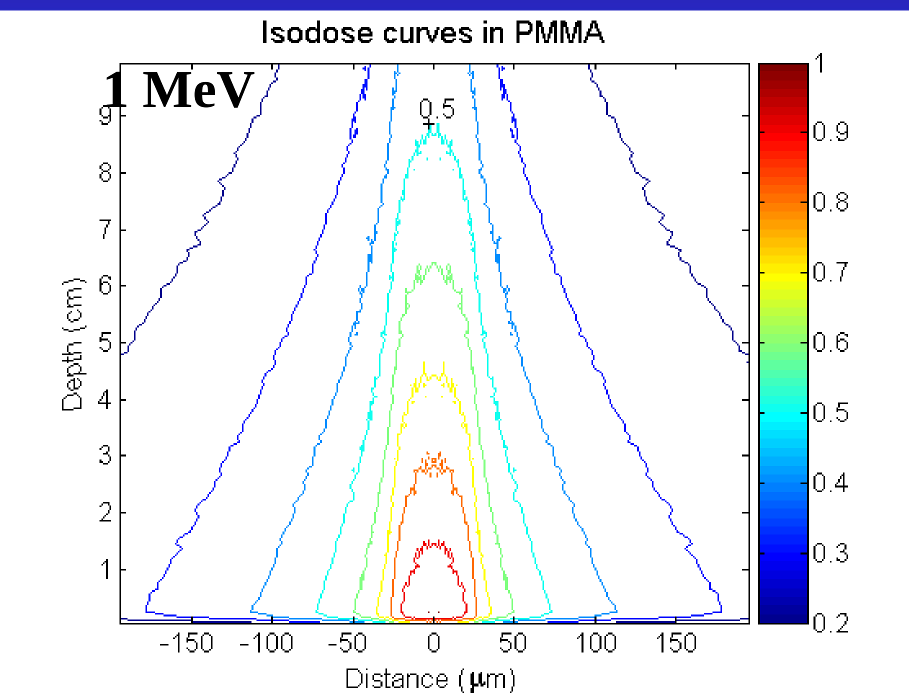


E. Siegbahn et al., Medical Physics 33 (9) 2006

J. Spiga et al., Medical Physics, 34 (11) 2007


Isodose curves in PMMA
ESRF
spectrum
Depth (cm)
Distance (μm)
0.5
-150 -100 -50 0 50 100 150
1 2 3 4 5 6 7 8 9
0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1


ESRF
spectrum
Relative dose (%)
Depth (cm)
Distance (μm)
0 20 40 60 80 100
10 5 0
-200 0 200
10 20 30 40 50 60 70 80 90 100


Isodose curves in PMMA
1 MeV
Depth (cm)
Distance (μm)
0.5
-150 -100 -50 0 50 100 150
1 2 3 4 5 6 7 8 9
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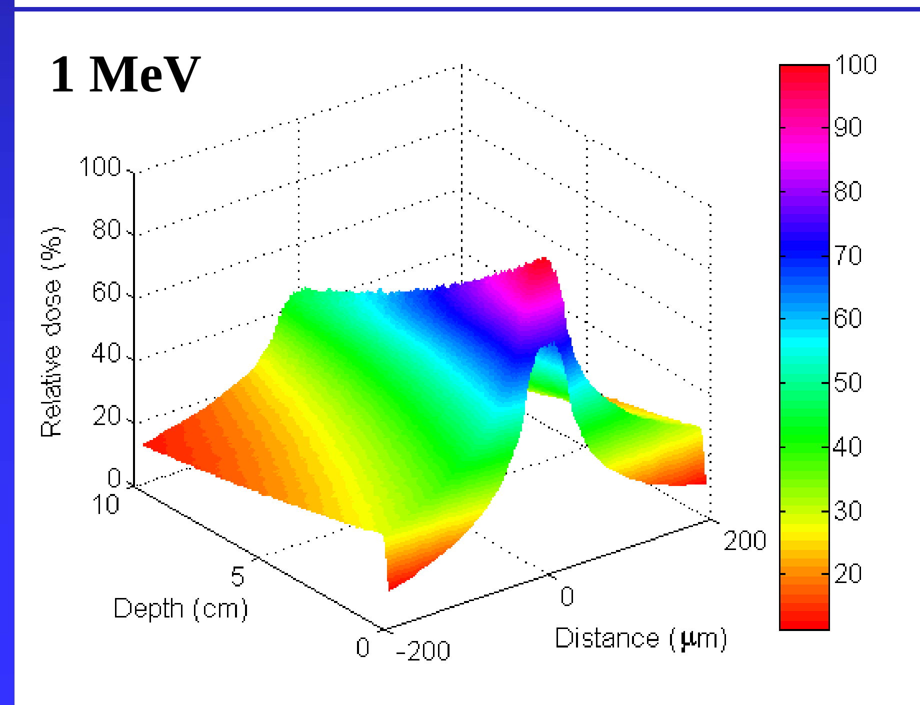
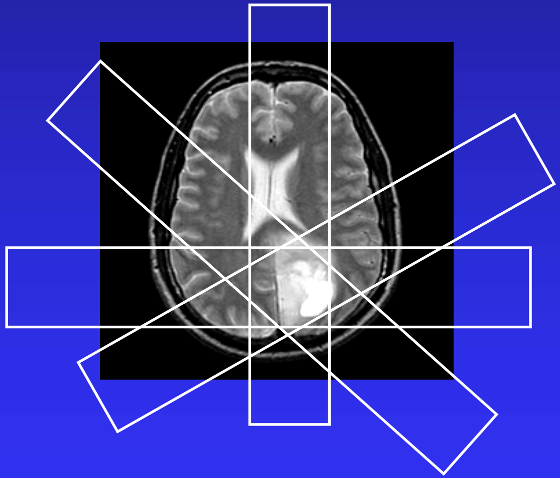

1 MeV
Relative dose (%)
Depth (cm)
Distance (μm)
0 20 40 60 80 100
10 5 0
-200 0 200
20 30 40 50 60 70 80 90 100

Stereotactic Synchrotron Radiation Therapy (SSRT)

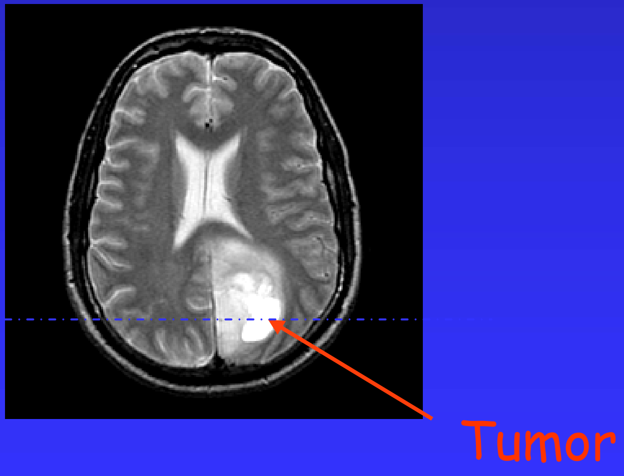
SSRT

- Principle:
  - Tumor loaded with a high Z element (iodine, gadolinium) + a chemotherapic drug (cis-platinum)
  - Beam size adjusted to the tumor dimensions
  - Tumor positioned at the center of rotation
  - Irradiation with kilo-Voltage X-ray beam



Iodine Dose Enhancement

- Tumor > Blood Brain Barrier disruption
- Accumulation of the contrast agent
- Tumor X-ray absorption cross section is increased ($Z_{iode} >> Z_{eq.water}$)



Dose Profile

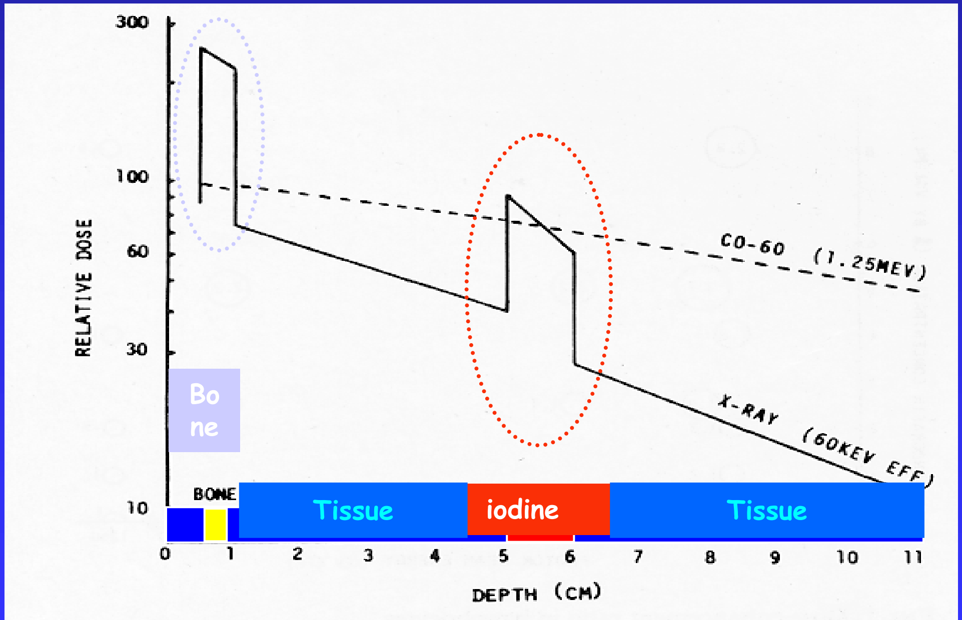
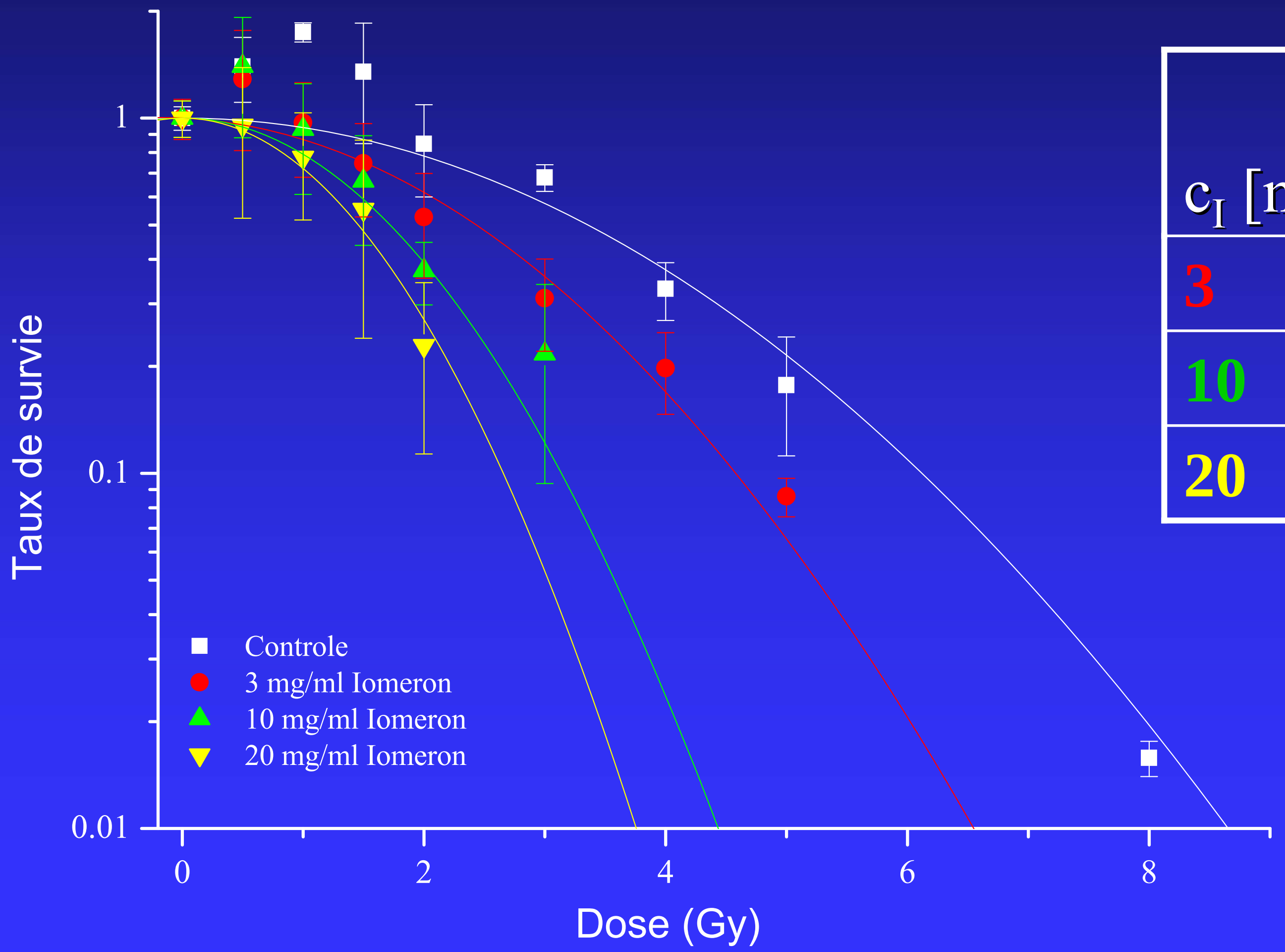


FIG. 2. Depth dose distribution (calculated).

Mesa AV et al. *Phys Med Biol* 1999;44:1955–1968.

Survival vs Iodine Concentration

- ✓ Just after irradiation ⇒ Cells were sub-cultured
- ✓ 15 days later ⇒ Colonies were stained and counted



c_I [mg/ml]
3
10
20

Energy: 50 keV

Preclinical studies

- Tumor model: F98 glioma
- Animal model: (Fisher) Rat

iodine…..

Tumor is irradiated (15 Gy) after infusion of iodine (2 ml, 350 mg/ml)

Enhancement life span: +170 %

JF Adam et al. Int J Radiat Oncol Biol Phys. 2005 61 (4) 1173-82
JF Adam et al. Int J Radiat Oncol Biol Phys. 2006 64 (2) 603–611

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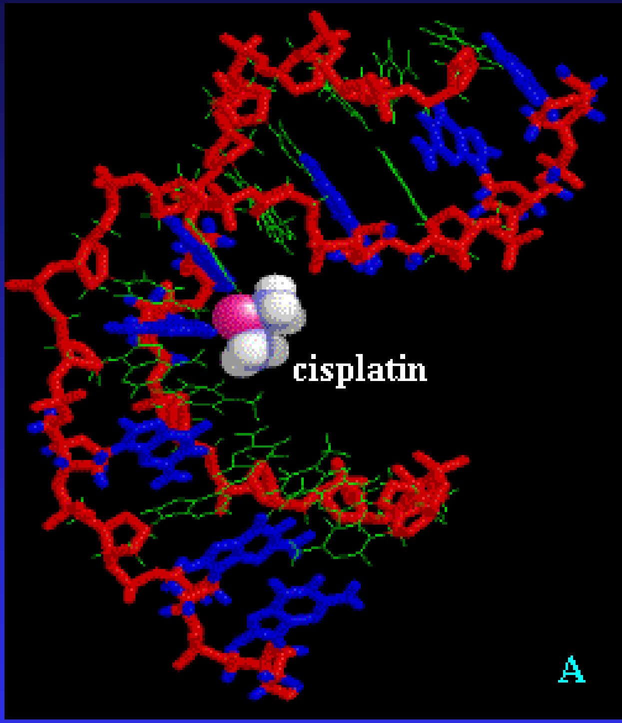
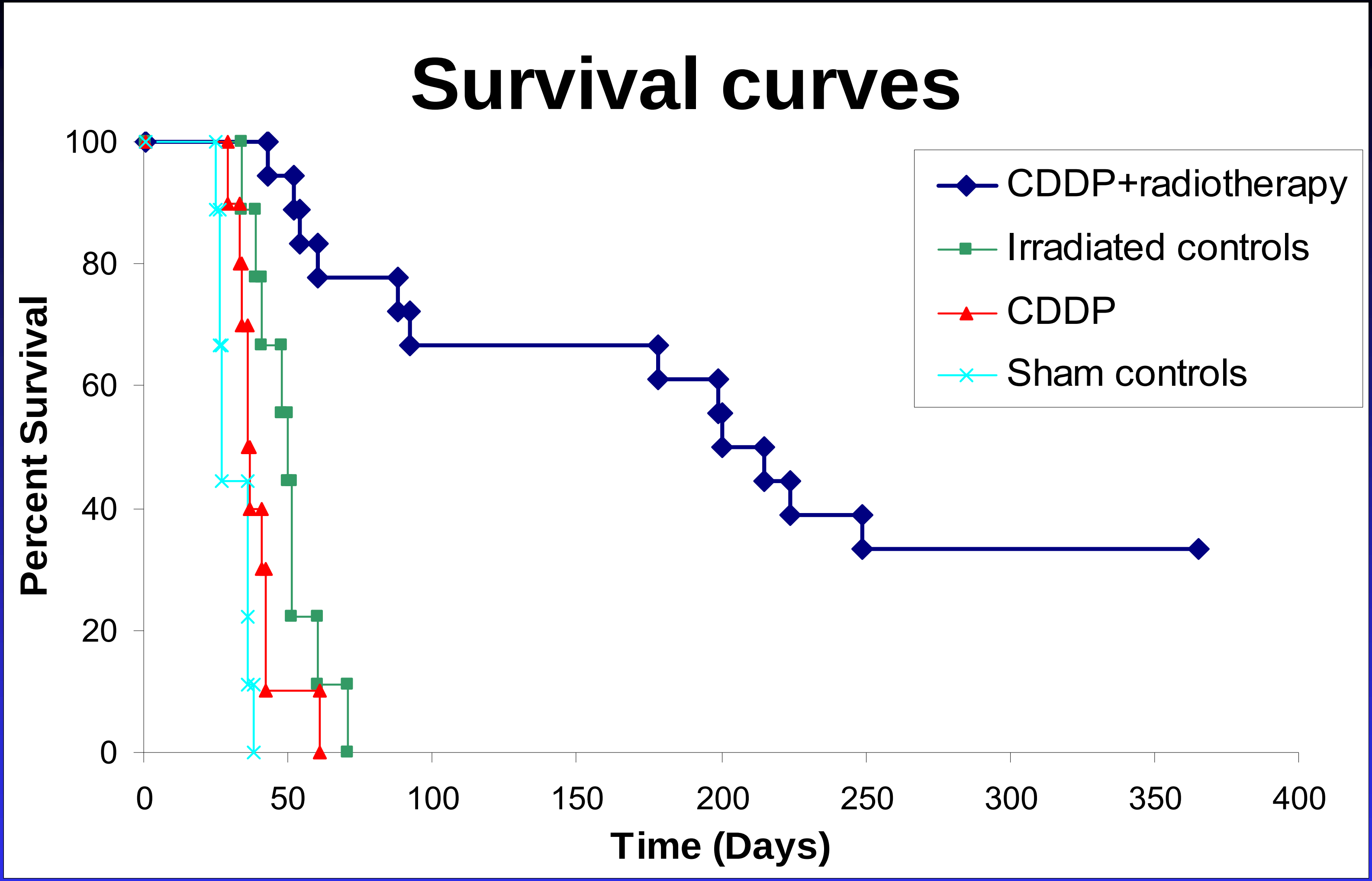
Inoculation of a Platinum compound (PAT)



- (CDDP)-Platinum compound
- Chemotherapy agent
- CDDP binds to DNA
- Intra-tumor injection of 3 mg CDDP in 5 ml, 13 days after tumour implantation
- Irradiation @78 keV - 15 Gy @ tumor - Day 14th



694 % Increase in life span relative to median survival time

M.C. Biston, et al., Cancer research, 64, 2317-2323 (2004)

Clinical perspective of MRT and SSRT at the ESRF

- Following excellent preclinical results, the ESRF and CHU Grenoble have decided to perform SSRT clinical trials at ID17. Phase I-II clinical trials will start in 2009.

- The ESRF has also decided to fully refurbish the MRT station for allowing testing the therapy in spontaneous tumours in dogs and cats as a milestone for deciding clinical trials in humans

Applications @ high intense compact sources

(my personal view in approximation 0)

Application	E_{min} (keV)	$(\Delta E/E)_{min}$	Min Beam size (cm^2)	High repetition Rate	Projection / CT mode	Impact (society, public..)
Clinical imaging: K edge subtraction (stroke, coronary angiography, aneurysm)	34	10^{-2}	2x2	+++	both	+++
Cl. mammography Propagation/ABI/gratings	20	$10^{-1}/10^{-4}/10^{-1}$	10x10	++	both	+++
Cl. imaging: cartilage Propagation/ABI/gratings	30	$10^{-1}/10^{-4}/10^{-1}$	5x5	++	both	++
Radiotherapy: dose enhancement	50	10^{-1}	2x2	+	projection	+++
Radiotherapy: microbeams	100	10	2x2	+	projection	+++
Radiobiology/bystander effect	5	10^{-1}	1x1	++	projection	+
Radiotherapy: IMRT	100	10	2x2	+	projection	+++

High intense table top quasi monochromatic source

(my personal view in approximation 0)

Application	E_{min} (keV)	$(\Delta E/E)_{min}$	Beam size (cm^2)	High repetition Rate	Projection/ CT mode	Impact (society, public..)
Microanalysis/quantification	5	10^{-1}	2x2	+	CT	++
Cultural heritage (K-edge imaging etc) on paintings	10	10^{-2}	2x2	+	Projection	++
Paleontology imaging CT (propagation)	20	10^{-1}	2x2	+	CT	++
SAXS						
Protein crystallography						
…						
…						

ID17 team

BMF Team

CHU/INSERM/UJF

ID21

Swiss based team for MRT

J. Dik, Univ. of Delft, NL

Thanks!