The Abdus Salam
International Centre for Theoretical Physics

United Nations
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Advanced School on Synchrotron and Free Electron Laser Sources and their Multidisciplinary Applications

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Application of x-ray imaging in Medicine

Giuliana Tromba
Sincrotrone
Trieste

Application of x-ray imaging in medicine

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SYRMEP Collaboration

Some applications at SYRMEP

Technique	Applications
Absorption	**Bones**, teeth studies
Contrast agent-based imaging (tracking studies using heavy elements, K or L edge imaging)	Angiography, bronchography, **brain studies(^)**
Phase Contrast imaging (PHC)	**Mammography, lungs**
Diffraction Enhanced Imaging (DEI)	**Cartilages**, **joints**, lungs, etc

(^) in combination with PHC imaging

I

Cell tracking studies for imaging of brain tumors in rats

Technique: Contrast agent (Gd) + PHC

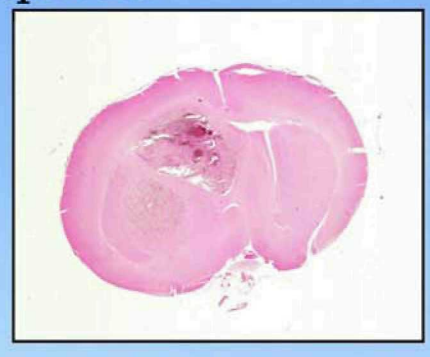
Image modality: micro-CT

Imaging of Brain Tumors

Glioblastoma multiforme (GBM) is the most common and most aggressive primary brain tumor in humans.
One reason for the high rate of recurrence is the invasive nature of the tumor into the surrounding normal brain tissue and its multifocal occurrence at sites remote from that of the primary tumor.
Animal model based on Wistar rats have been developed to study the behavior of the tumor and to monitor the effects of therapies.

Requirements for the cell tracking technique:
- to monitor the dynamic of tumour growth
- to follow the migration of tumour cells
- to understand the dynamic of metastasis spread

Section of healthy rat brain



Section of rat brain with C6 glioma 2 weeks after implantation

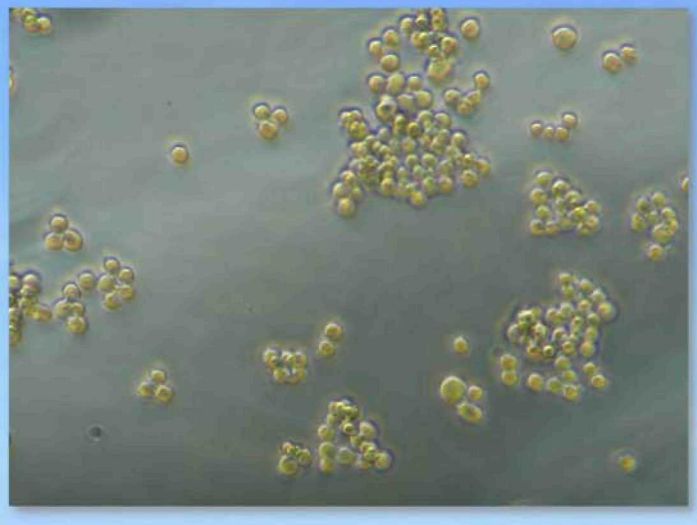
E. Schultke, R.H.Menk et al.

Imaging of Brain Tumor

C6 glioma cells were cultured and some of the cultures were exposed to colloidal Gold Nano Particles (GNP) for 22 hrs before harvest.

C6 glioma cells were implanted into the brain of adult male Wistar rats. The implantation was performed with the animals under general anesthesia. The animals were allowed to recover after the end of the implantation and were sacrificed two weeks later.

We then employed SR CT technique to image the tumor. The detection of labeled cells is enhanced by the higher absorption of gold with respect to tissue and by PHC effects.



Gold Nano particles (GNP)

Our biological approach: Label cells with sufficient Au nano particles (Ø ~50 nm)

Inert GNP bond to serum proteins

GNP are taken up by phagocytosis stored in lysosomes and are not released by exocytosis

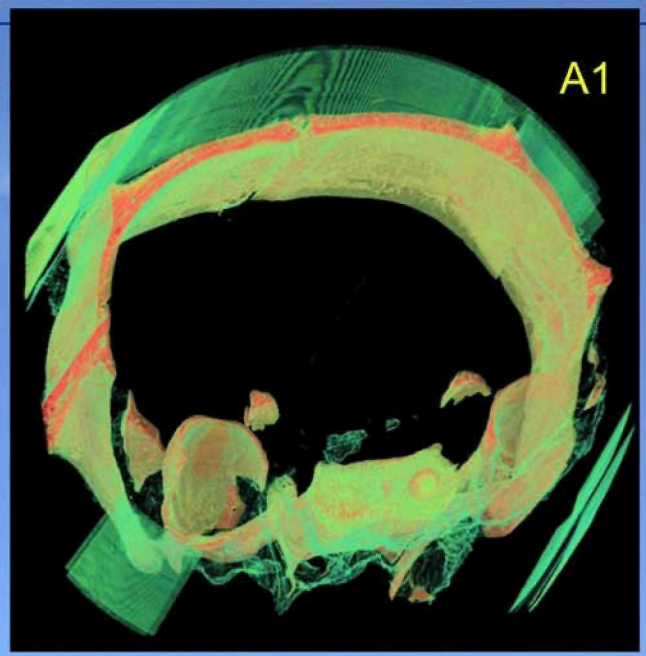
E. Schultke, R.H.Menk et al.

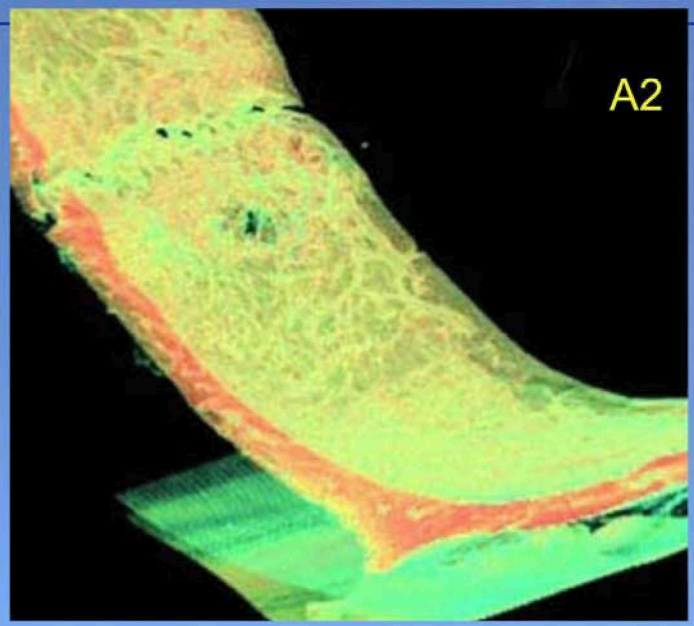
Courtesy of E. Schultke, R.H.Menk et al.

A 1 and A 2: Tumor without colloidal gold

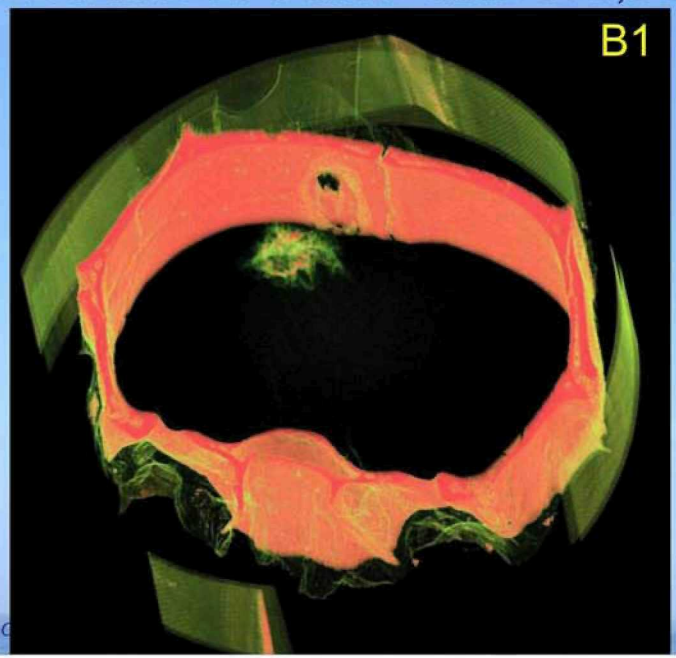
3D rendering of a 4 mm thick volume

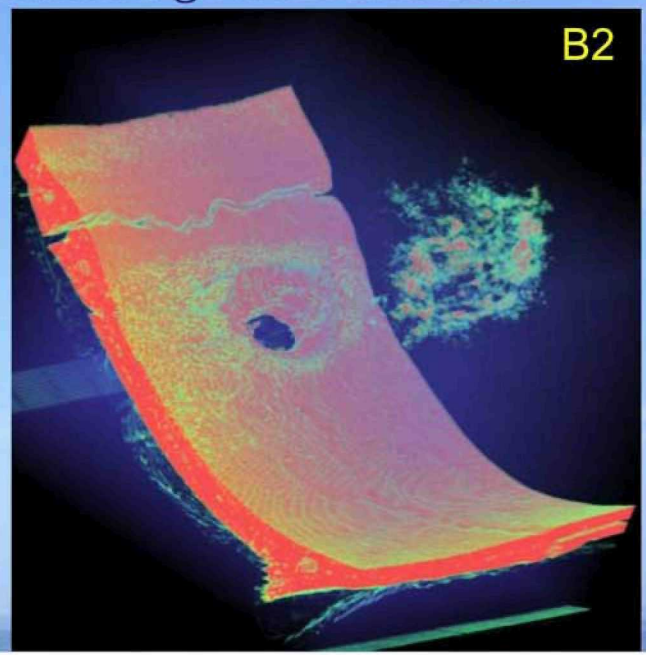
E = 24 keV
Num. proj. = 720
Pixel size =14μm





B 1 and B 2: Tumor with 300,000 colloidal gold-loaded cells





II

Mammography: in vivo trial with patients

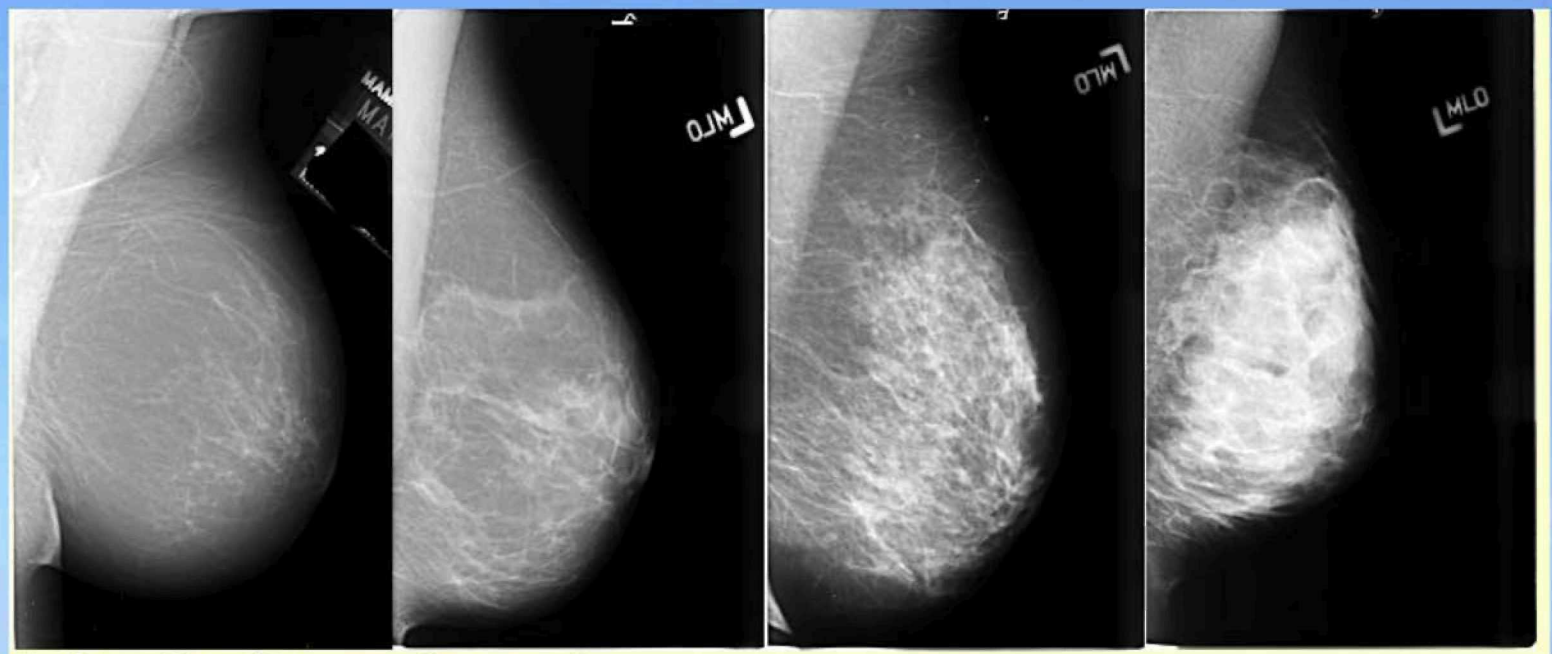
Technique: PHC

Image modality: planar

Breast imaging

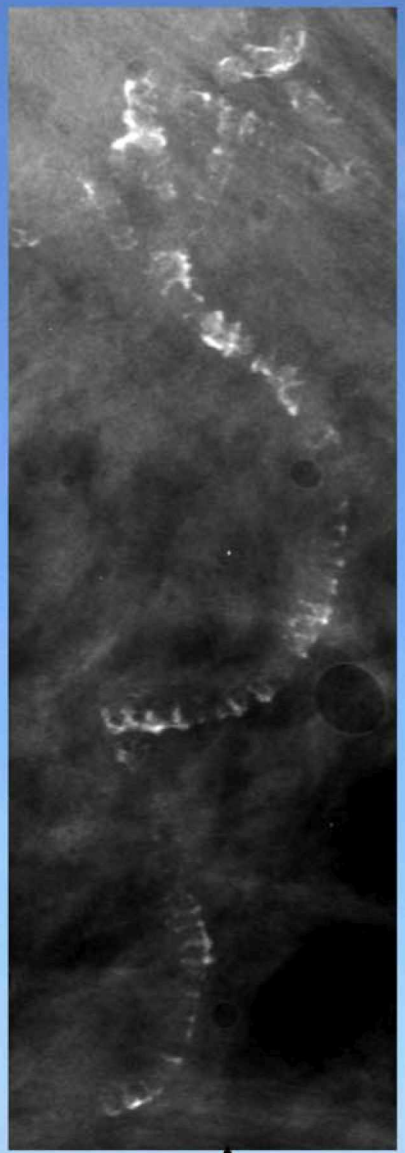
- Breast cancer is the most common cancer amongst women (incidence: 8%)
- The success of treatment depends on early detection (asynthomatic women)
- Main method for detecting early breast -> **X-ray mammography**
- Screening programs for large population area above 50 years old
- Sensitivity of conventional mammography: 85-90%, Specificity: 90%
- False positive/true positive ≈ 5 -10%
- High number of doubtful cases makes frequent the need of biopsies
- Conventional mammography is **not enough effective** for dense breasts

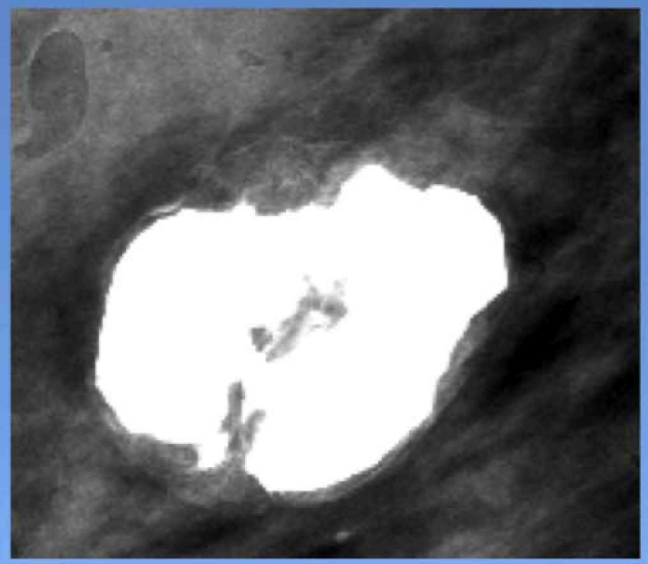
Radiographs of breasts with increasing density: mainly adipose breast (left) up to high fibro-glandularity breast (right)

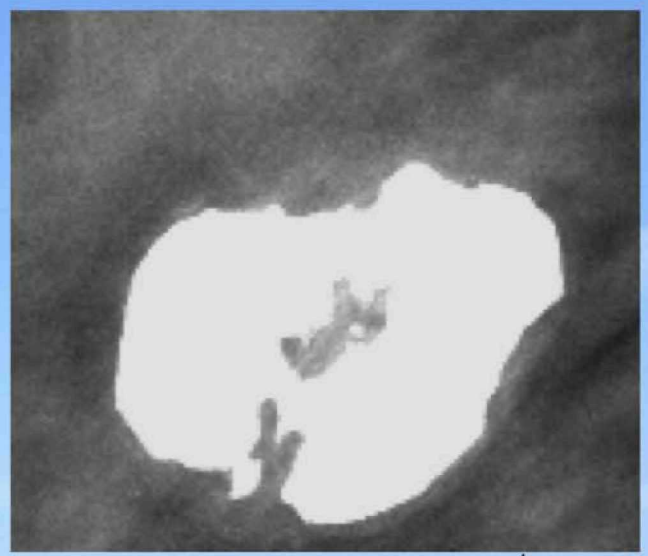


Breast composition and its mammographic appearance.[1]

PHC application to mammography: Human tissue sample







SR

E = 17 keV

Thickness = 4 cm
MGD = 1.5 mGy

E = 17 keV

SR

Conventional X-ray generator

30 kVp, 50 mAs

The SYRMA project
(**SY**nchrotron **R**adiation for **MA**mmography)

Agreement among the Public Hospital of Trieste, the University of Trieste and Elettra

Aim -> *In vivo* mammography studies on cases selected by the Radiologist.

Target-> Dense breasts;

conventional radiographs with uncertain diagnosis;

suspect of false positives.

Set-ups-> I Phase: PHC radiography with commercial detectors;

II Phase: low-dose tomography with custom Si microstrip detector.

Clinical trial started on March 13, 2006

Patients' selection

The patient recruitment is performed on the basis of the BI-RADS classes of the American College of Radiology (recognized by the European Guidelines for breast screening). A patient is a candidate suited to SR:

- When mammography shows a dense disomogeneous breast and ultrasonography does not solve the problem - Class R1
- When mammography shows an asymmetry of the two breasts, not understood by ultrasonography - Class R3
- When both mammography and ultrasonography are uncertain - Class R3 and R4.

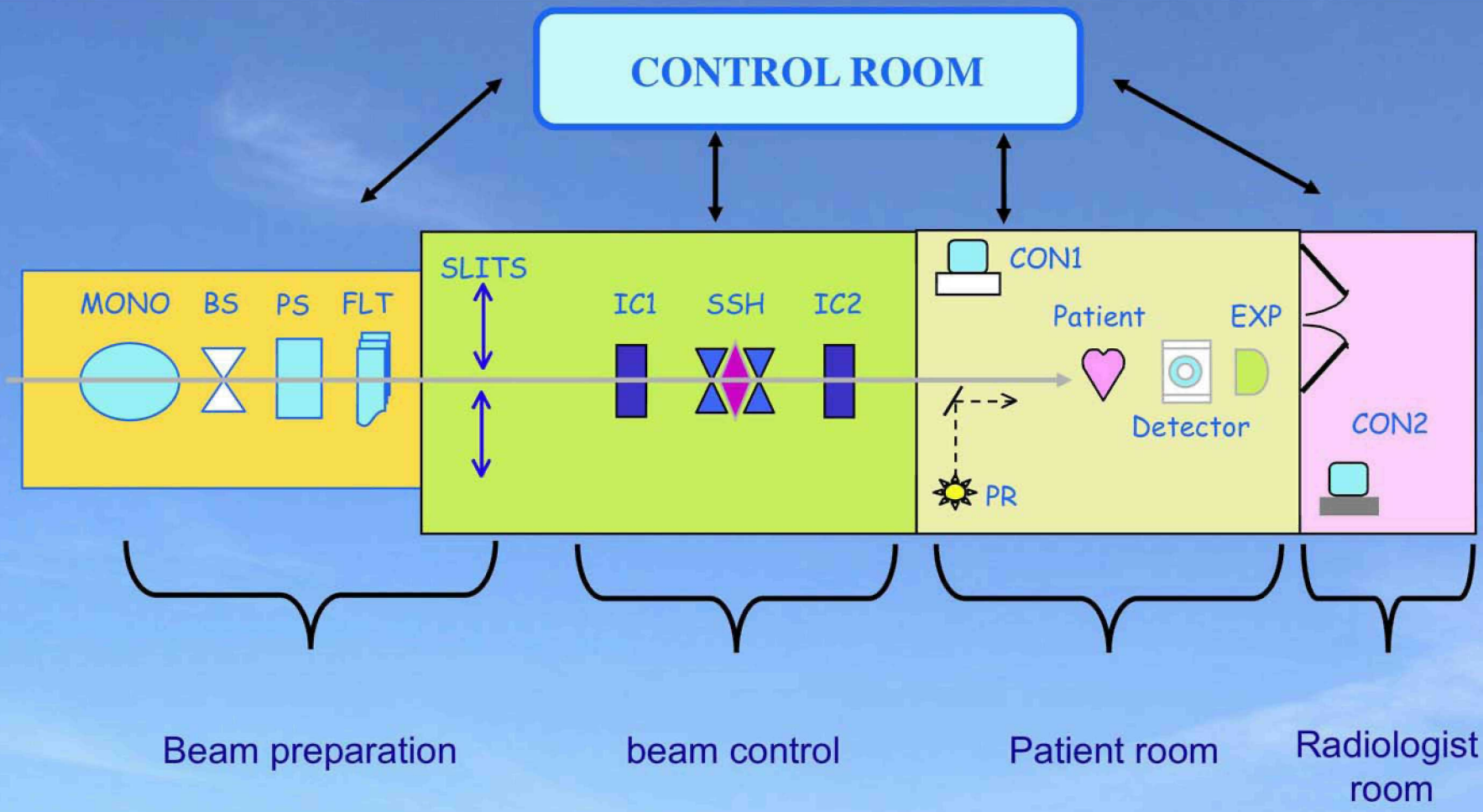
Methods used for comparing SR vs. conventional images

Better lesions characterization

Enhanced visibility of microcalcifications

Detectability of new lesions

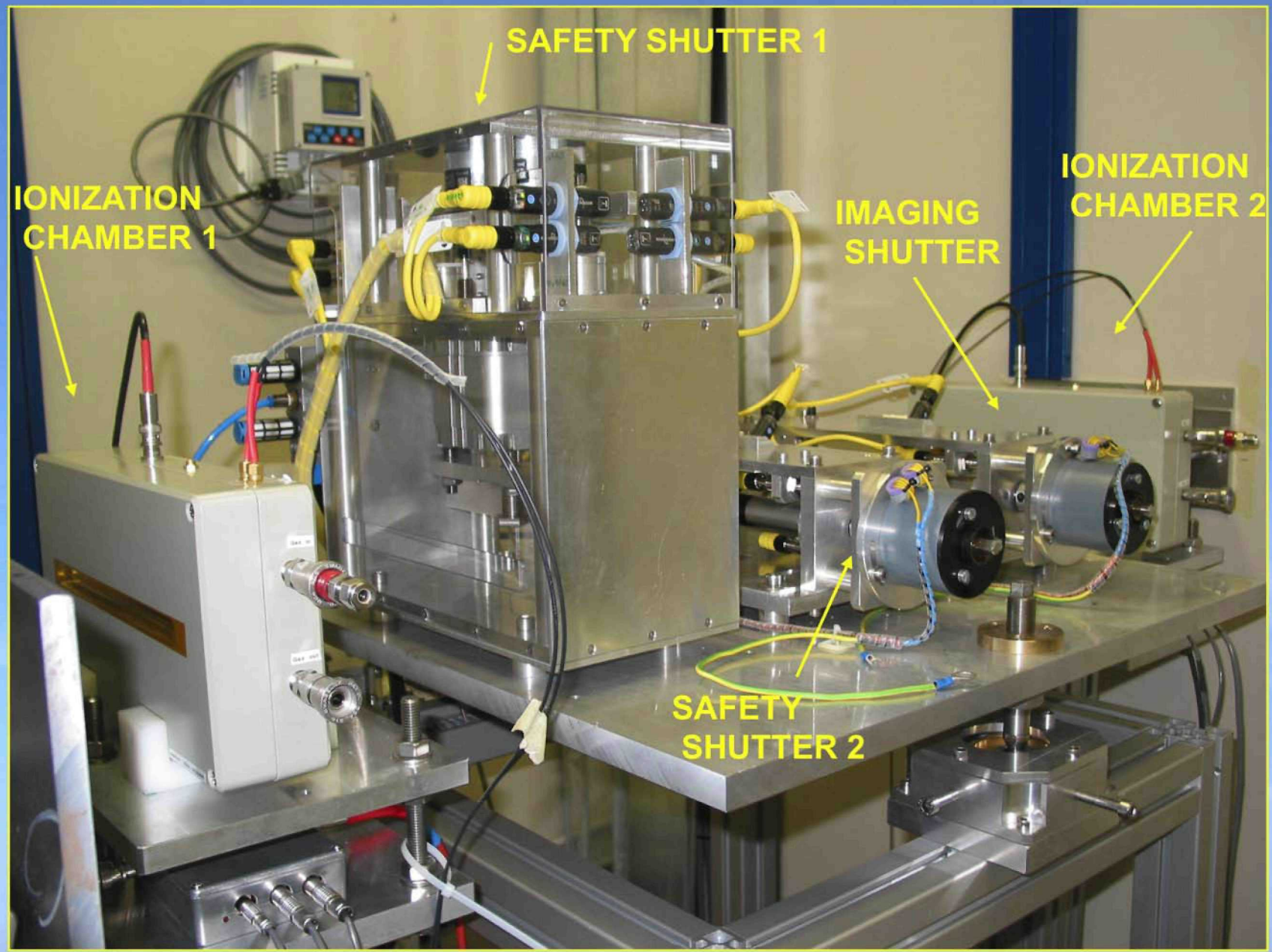
The SYRMA beamline



Safety systems:

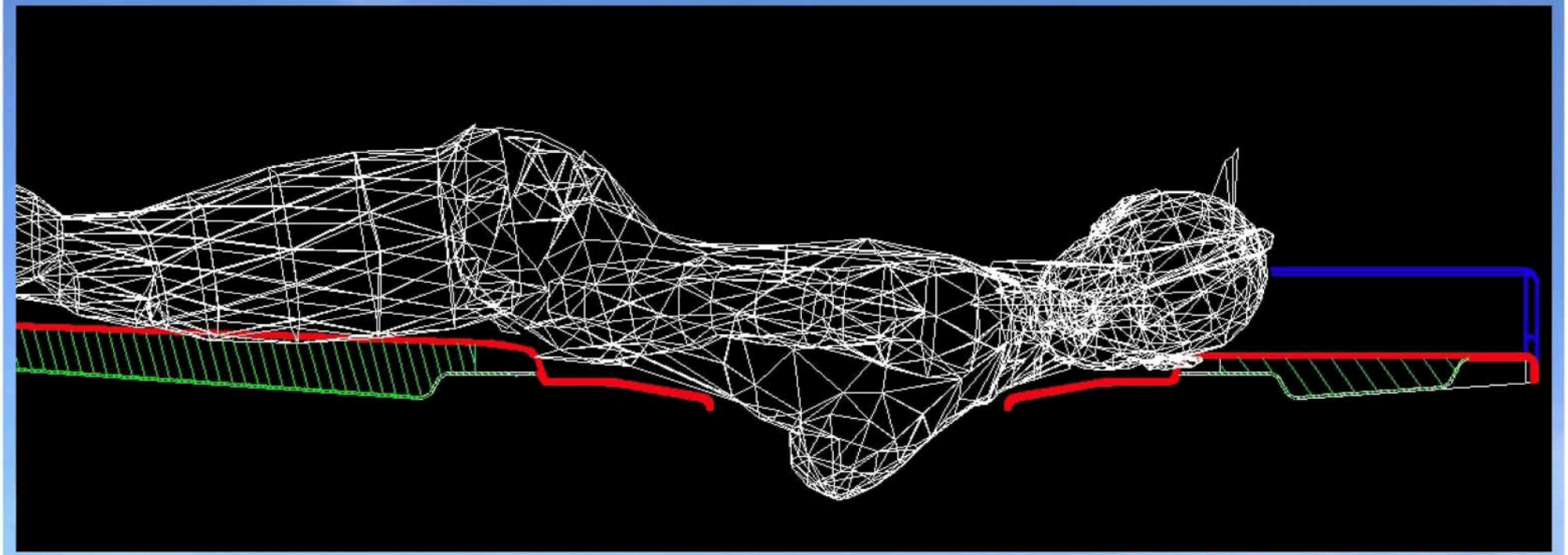
- Beamline access control system (for personnel)
- Dose control system (for patient)

Dose monitoring and shutters



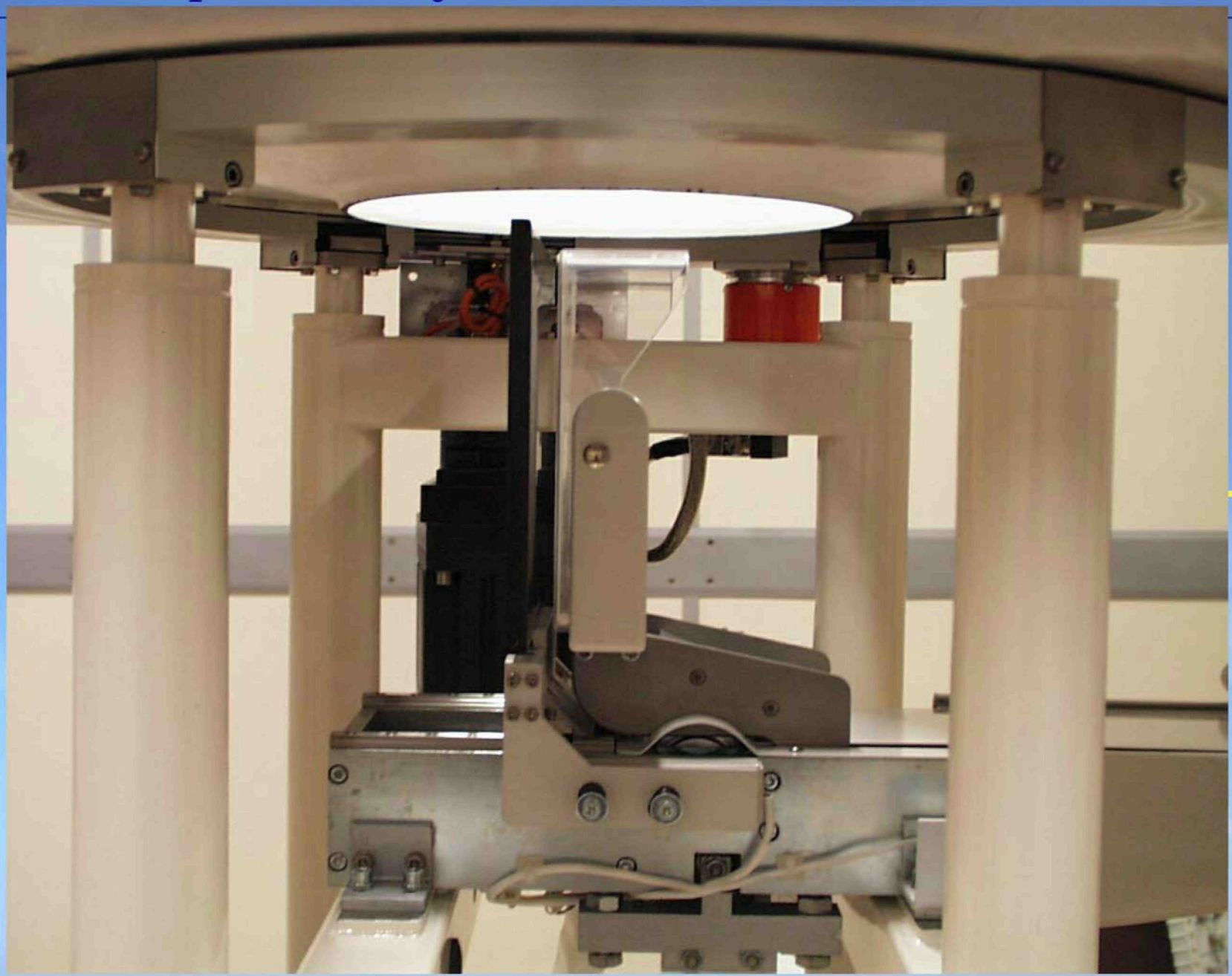
Radiologist room

Patient positioning

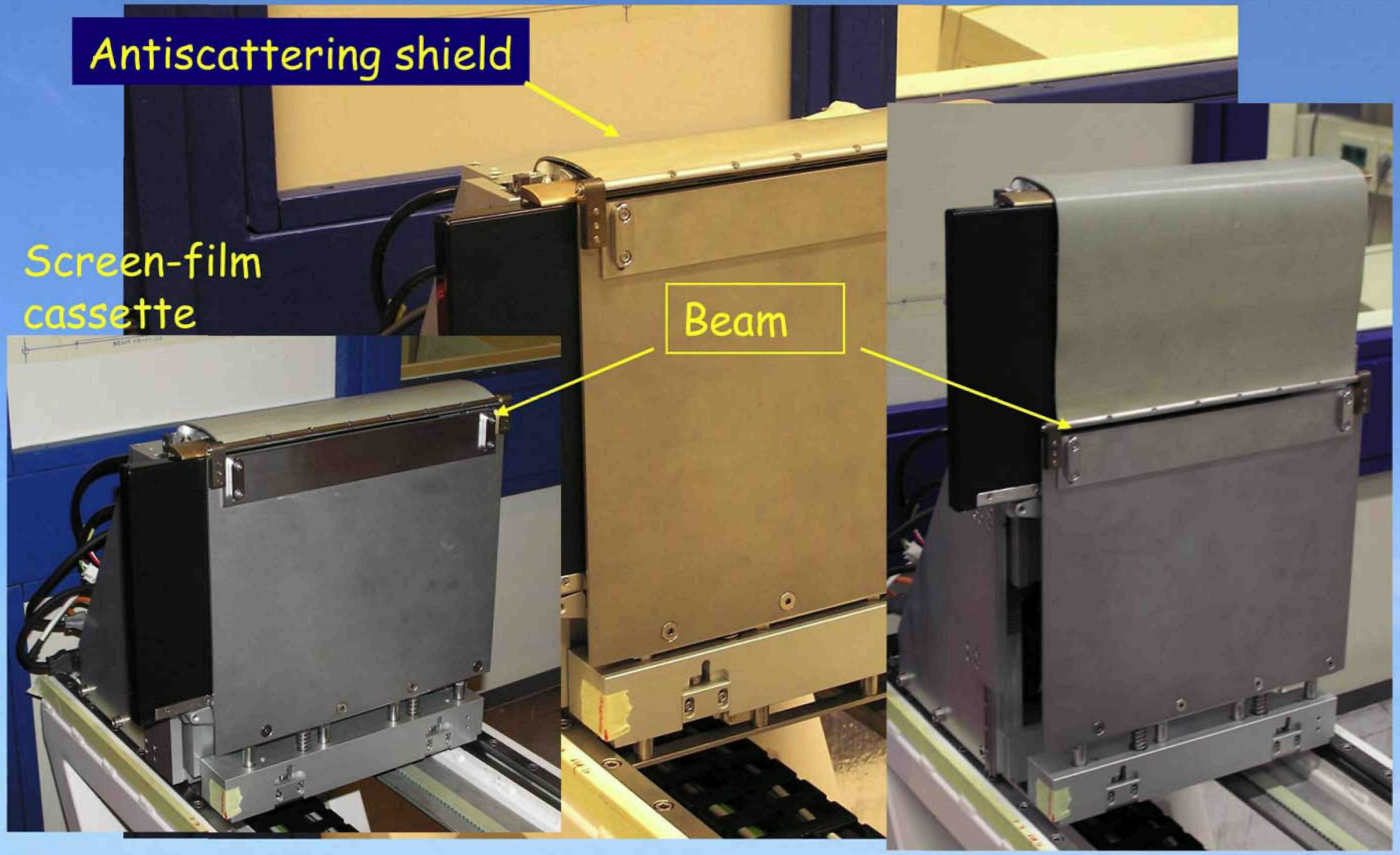


Patient support

Compression system



Detector holder



Procedures (controlled by examination Supervisor)

Exam initialization

- Input of patient parameters,
- Choice of X-ray energy (according to the breast thickness and on an estimate of breast glandularity class (i.e. low, medium, high)),
- Beam optimization.

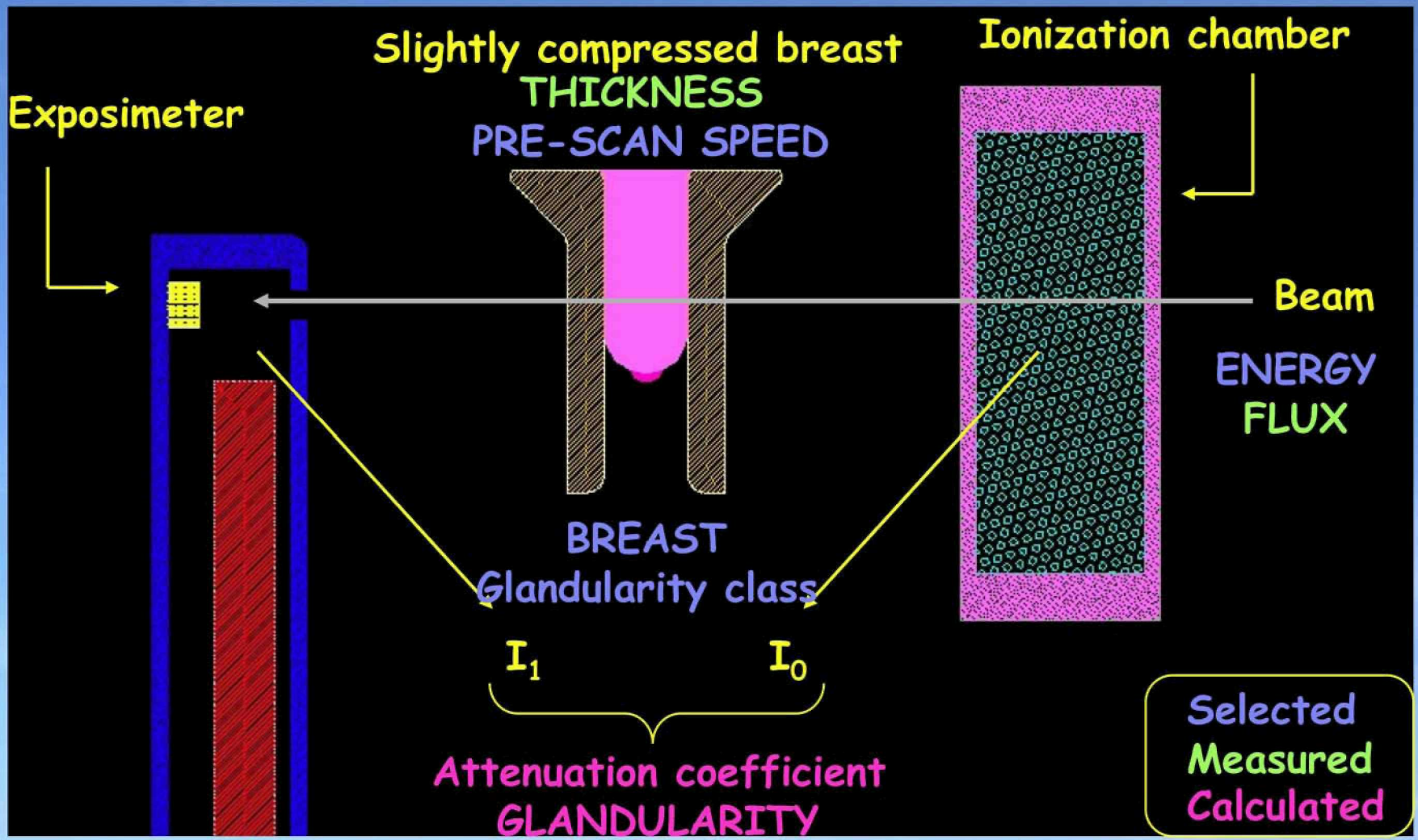
Prescan

- It is a scan over a small breast portion in a range selected by radiologist.
- It aims to measure the breast absorption properties and to evaluate the real breast glandularity.
- The results of prescan are used to confirm the choice of the X-ray energy and to calculate the scan speed.
- The delivered dose is 5-10 % the examination dose.

Exam

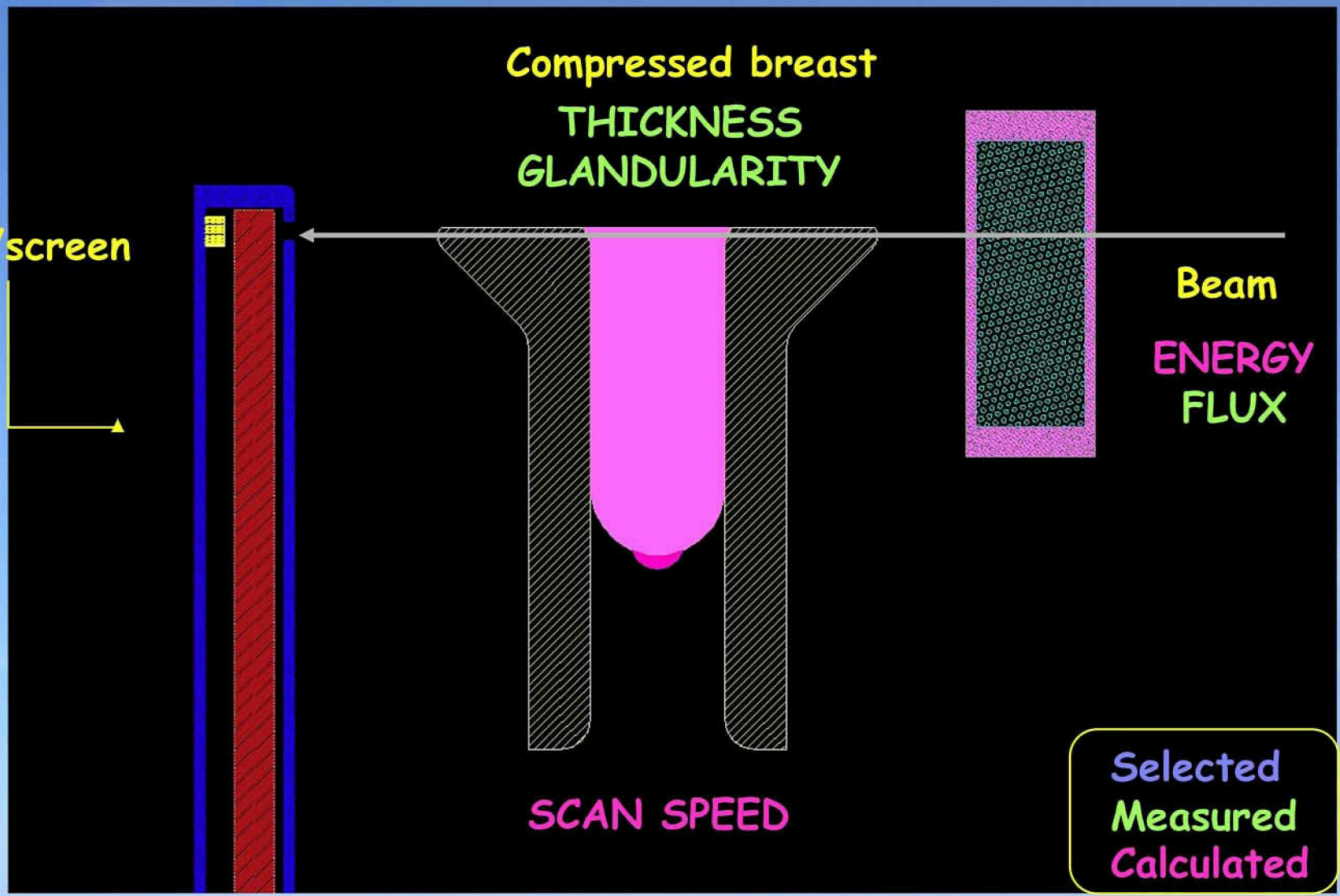
- The exam is a simultaneous scan of breast and detector in a range selected by radiologist.

Examination protocol: pre-exposure



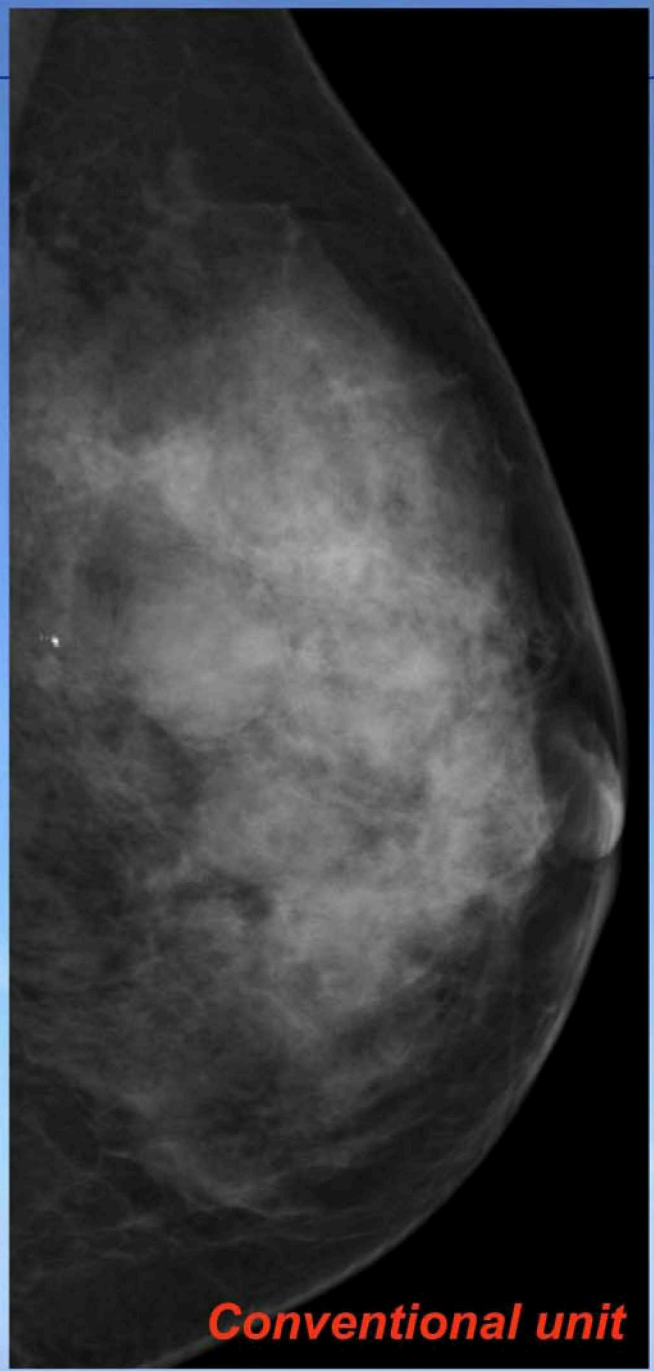
Film is removed from the beam

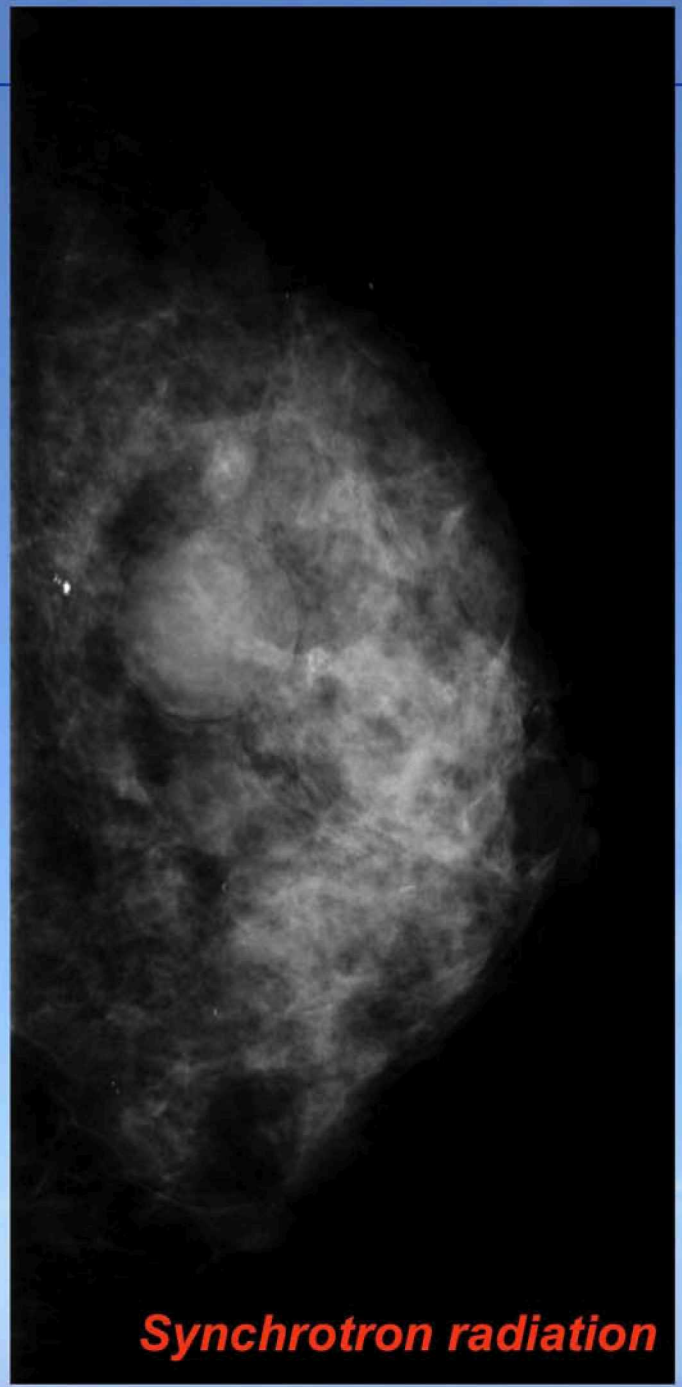
Examination protocol: exposure



Film in the beam

Pat. 8 - 164839 – GA – CC RIGHT s

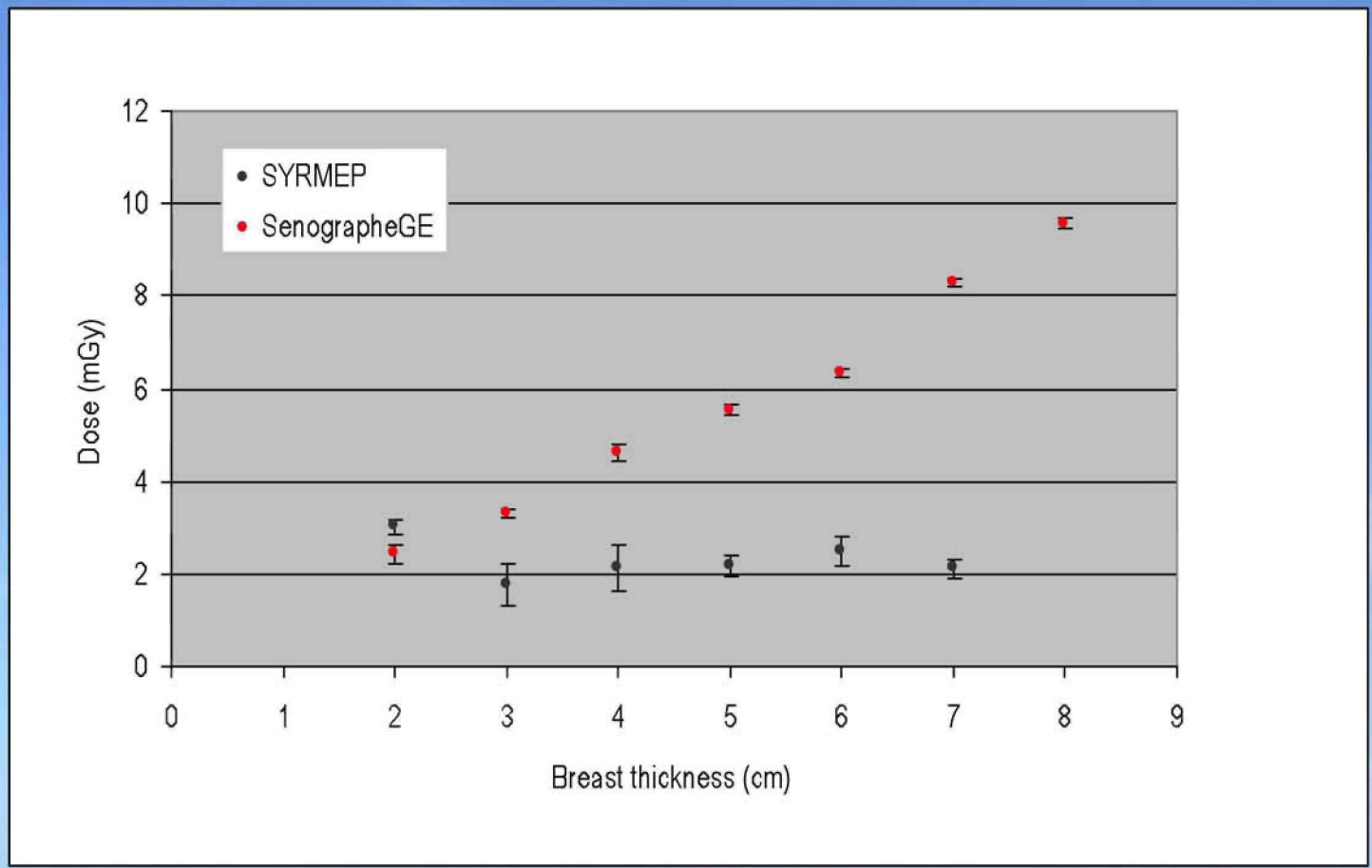




Doses comparison I

Average Entrance Skin Doses delivered to patients at SYRMEP and at the conventional mammographic unit (Senographe GE)

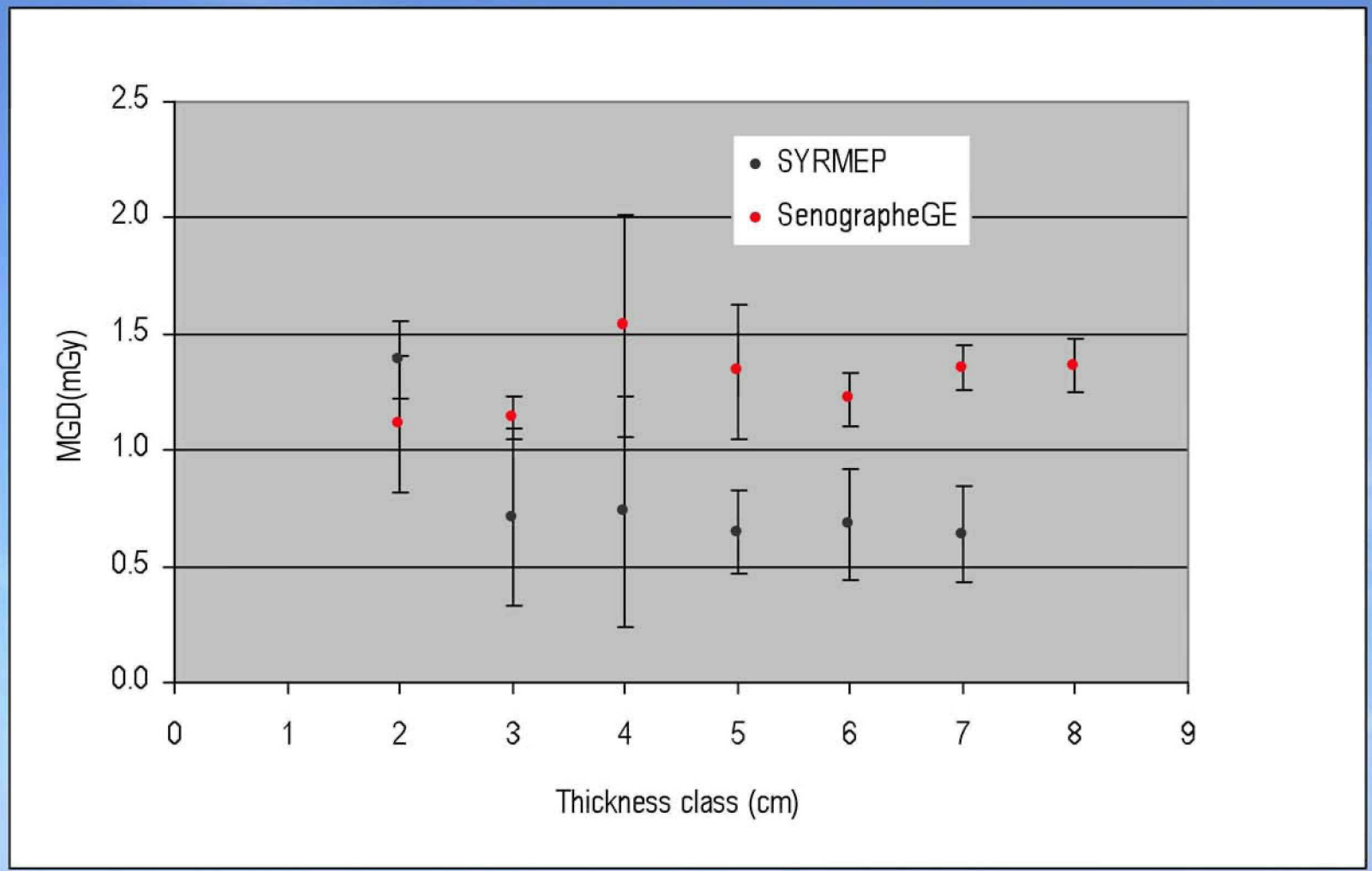
Vertical bars indicate the data distribution of each thickness class



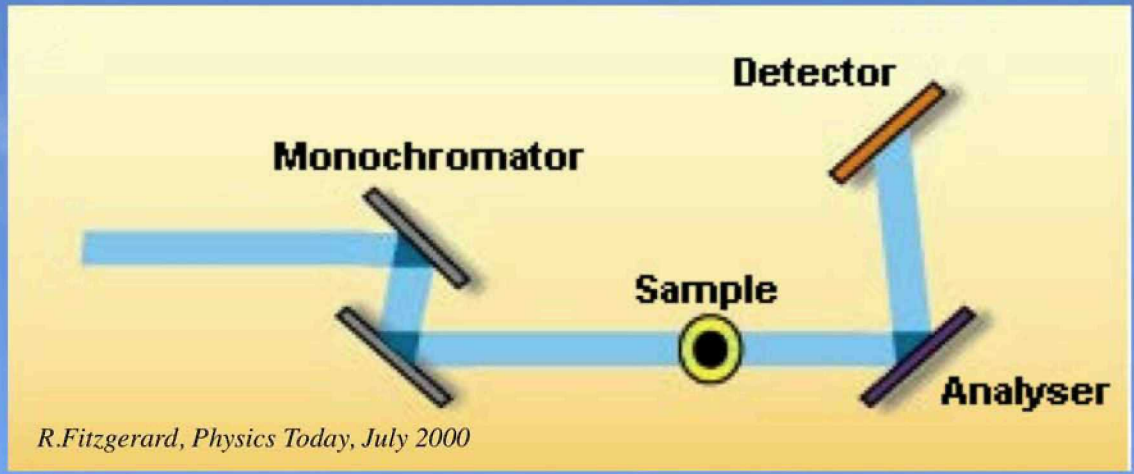
Doses comparison II

Average Mean Glandular Doses delivered to patients at SYRMEP and at the conventional mammographic unit (Senographe GE)

Vertical bars indicate the data distribution of each thickness class

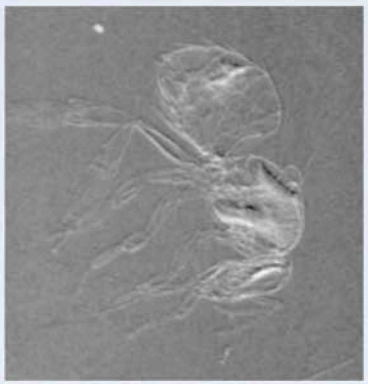


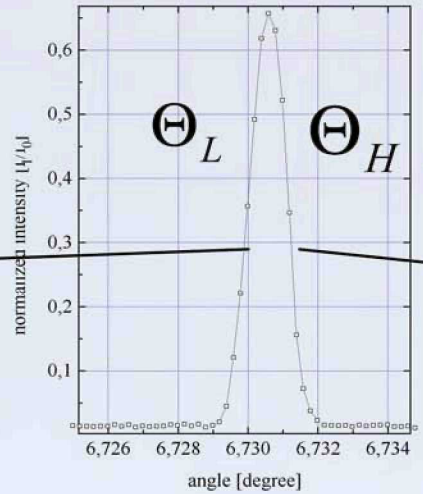
Diffraction Enhanced Imaging (DEI)

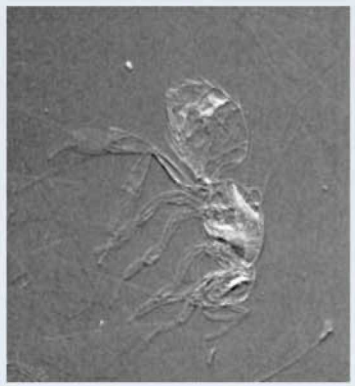


- A perfect crystal, positioned between sample and detector, is used as an angular filter to select angular emission of X-rays. The filtering function is the rocking curve (FWHM: 1-20 μrad)
- Image formation with DEI is sensitive to a variation of δ in the sample. Indeed, refraction angle is roughly proportional to the gradient of δ
- Analyzer and monochromator aligned -> X-ray scattered by more than some tens μrad are rejected
- Small misalignements -> investigation of phase shift effects
- With greater misalignements the primary beam is almost totally rejected and pure refraction images are obtained
- Sensitive to $\nabla\Phi(x,y)$

DEI image manipulation (Original Algorithm)







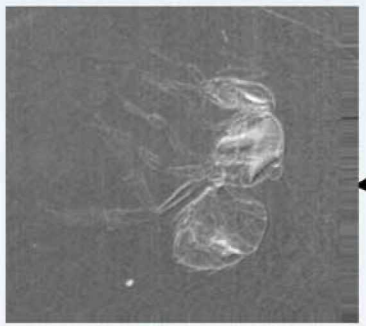
I_L I_H

$$I_L = I_R\left(R(\Theta_L) + \frac{\partial R}{\partial \Theta}(\Theta_L)\Delta\Theta_z \right)$$

$$I_H = I_R\left(R(\Theta_H) + \frac{\partial R}{\partial \Theta}(\Theta_H)\Delta\Theta_z \right)$$

Θ_Z = refraction Image

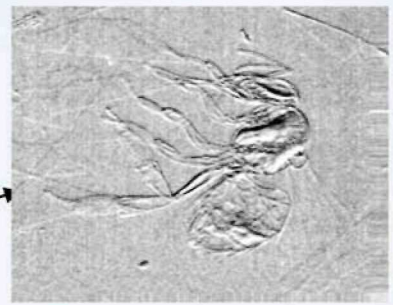
I_R = apparent absorption image (absorption +extinction)



Apparent Absorption Image

$$I_R = \frac{I_L \cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_H} - I_H \cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_L}}{R(\Theta_L)\cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_H} - R(\Theta_H)\cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_L}}$$

$$\Theta_Z = \frac{I_H \cdot R(\Theta_L) - I_L \cdot R(\Theta_H)}{I_L \cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_H} - I_H \cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_L}}$$



Refraction Image

Ref: Chapman et al, Phys.Med.Biol, 42,1997

III

Studies of cartilages and joints

Technique: DEI

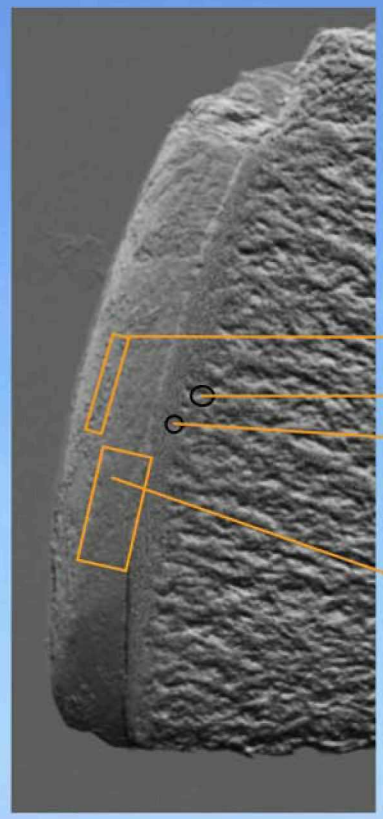
Image modality: planar

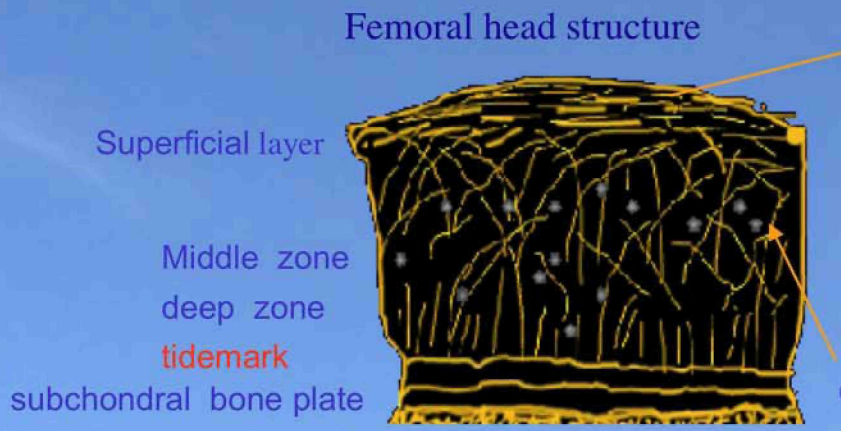
Study on cartilage/bone interface

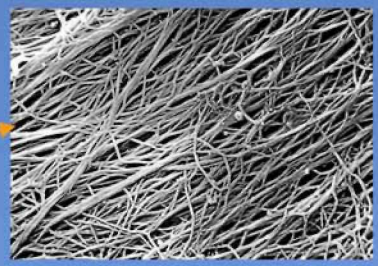
- Osteoarthrosis (OA) is a disease characterized by the progressive degeneration of articular cartilage and the development of altered joint congruency.
- Incidence: 14% of the adult population.
- Conventional radiography detects only important osseous changes. Early changes in the cartilage and other articular tissues are not directly visible.
- Cartilage loss can only be indirectly inferred by the development of joint-space narrowing which can be highly unreliable, False positives: 20-40%.
- Need to monitorate: soft articular tissues, cartilages, early changes in the adjoining subchondral and trabecular bone. Articular cartilage and subchondral bone act in concert with regards to the mechanical loading of the joint.

Study on cartilage/bone interface

Study of:
- cartilage
- cartilage bone interfaces
- changes in the bone structure







Electron microscope image of collagen fibers in the articular zone

Superficial Layer (Zone of horizontal collagen fibers with flat cells)

Subchondral Bone Plate (**Important for diagnostic purposes in osteoarthritis**)

Tidemark (Border between normal and mineralized cartilage)

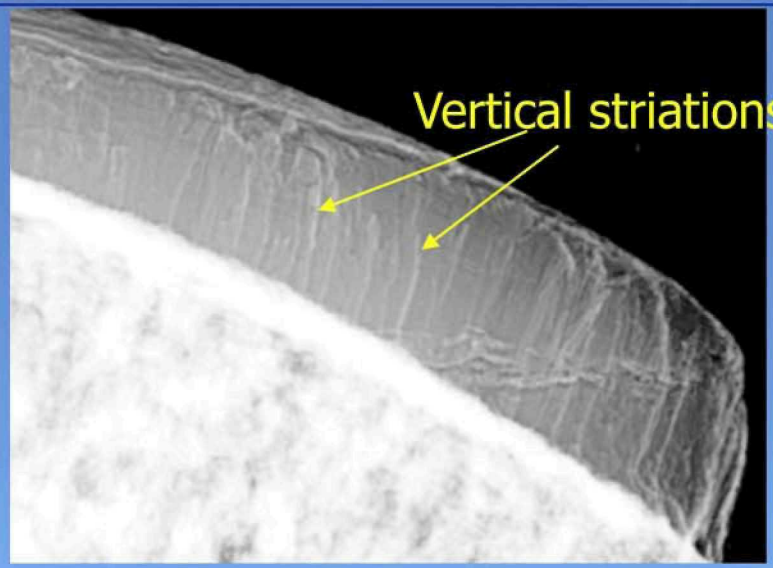
Transitional and Deep Layer (round cells, collagen fiber switches from horizontal to vertical orientation, increasing stiffness and material density)

Aim: detect the architectural arrangement of collagen within cartilage and evaluate how the cartilage degeneration affects the underlying subchondral and trabecular bone.

Muehleman C, Majumdar S. et al.

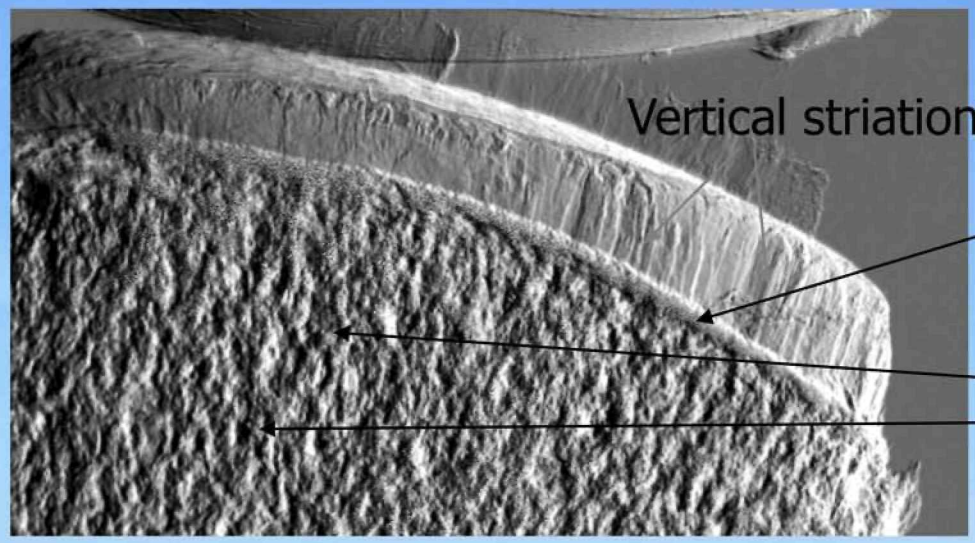
Femur head core cuts: collagen arcades structure

- The DEI technique allows to visualize the discontinuities of the sample and the inner structures invisibles by means of conventional X-Ray imaging.
- The transition bone-cartilage is emphasized.
- The articular cartilage striations are well visible due to X-ray diffraction at edges of fibers



Apparent absorption image

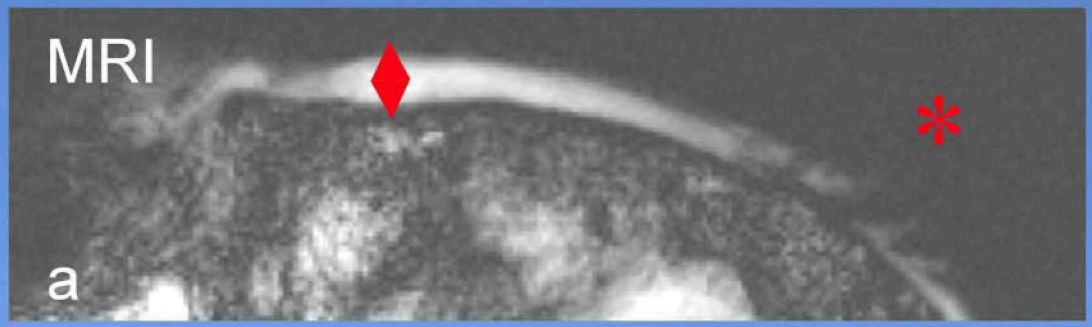
Refraction image



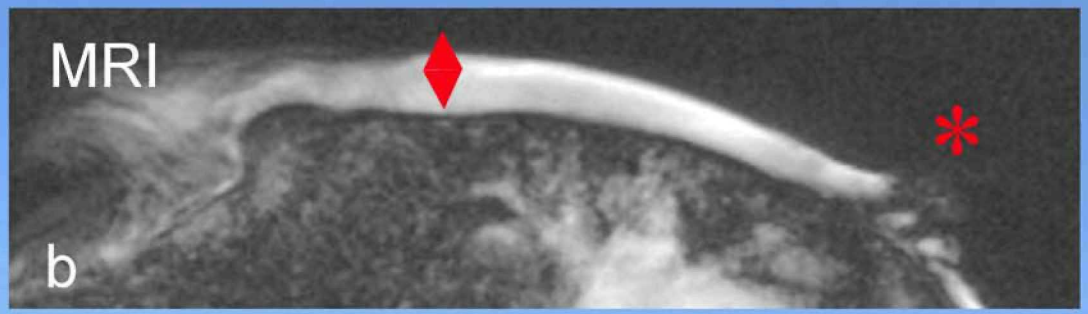
Elettra
25 keV

Muehleman C, Majumdar S, Issever AS, Arfelli F, Menk RH, Rigon L, Heitner G, Reime B, Metge J, Wagner A, Kuettner KE, Mollenhauer J, Osteoarthritis and Cartilage 12 (2): 97-105 FEB 2004

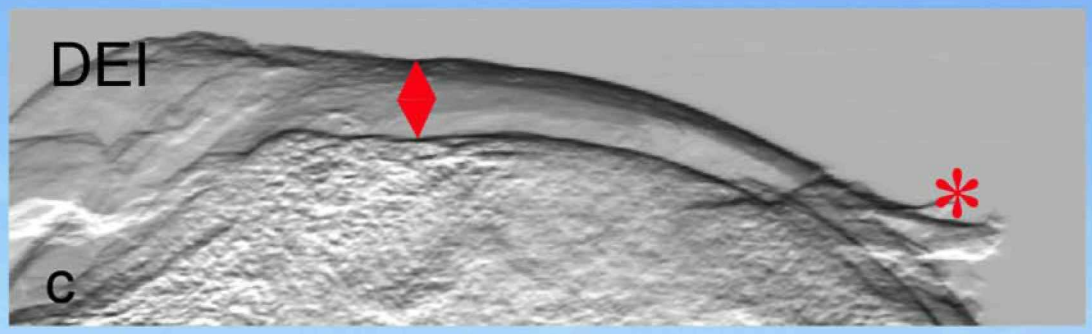
Femur head core cuts: comparison with MRI



5 sec

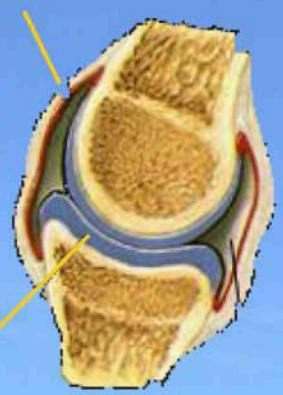


150 sec



A Wagner, M Aurich, N Sieber, M Stoessel, WD Wetzel, K Schmuck , M Lohmann, B Reime, J Metge, P Coan, A Bravin, F Arfelli, L Rigon, RH Menk, G Heitner, T Irving, Z Zhong, C Muehleman, J A Mollenhauer sumbitted to NIM A

Finger Joint



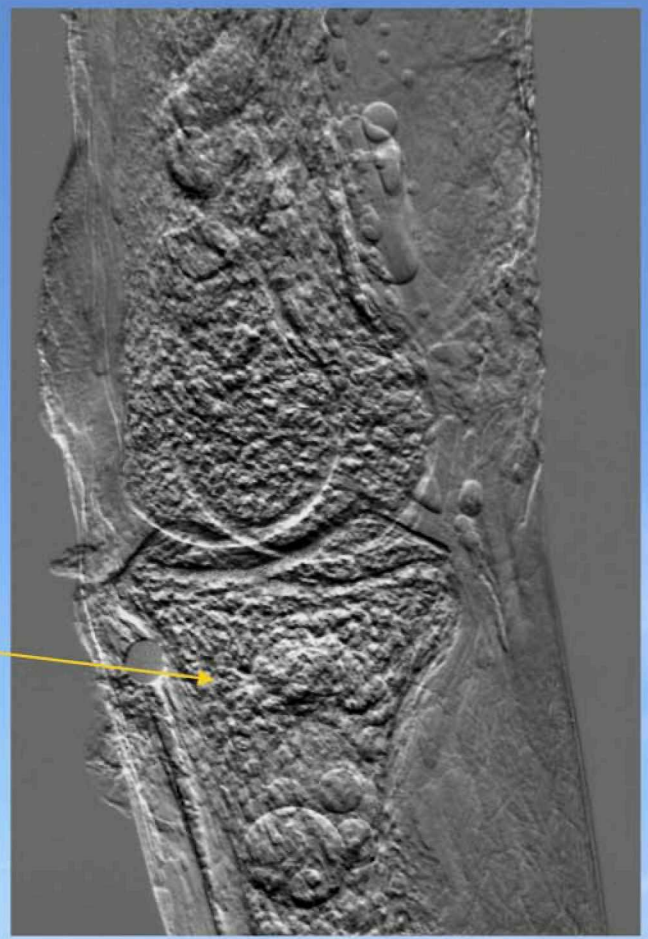
Conventional radiograph

Apparent absorption image @ 20 keV
at ELETTRA

R. Lewis, C.Hall, R.H.Menk et al.

Index finger proximal interphalangeal joint

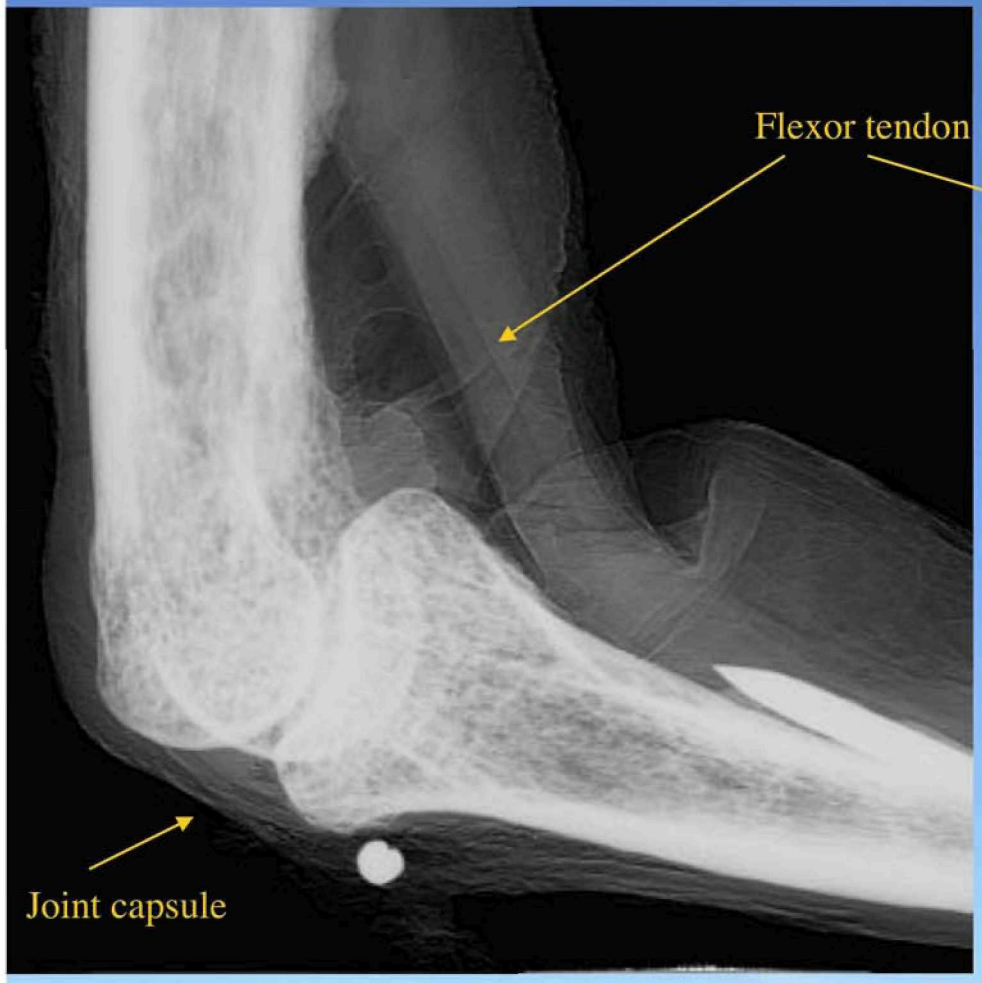
Apparent absorption Image



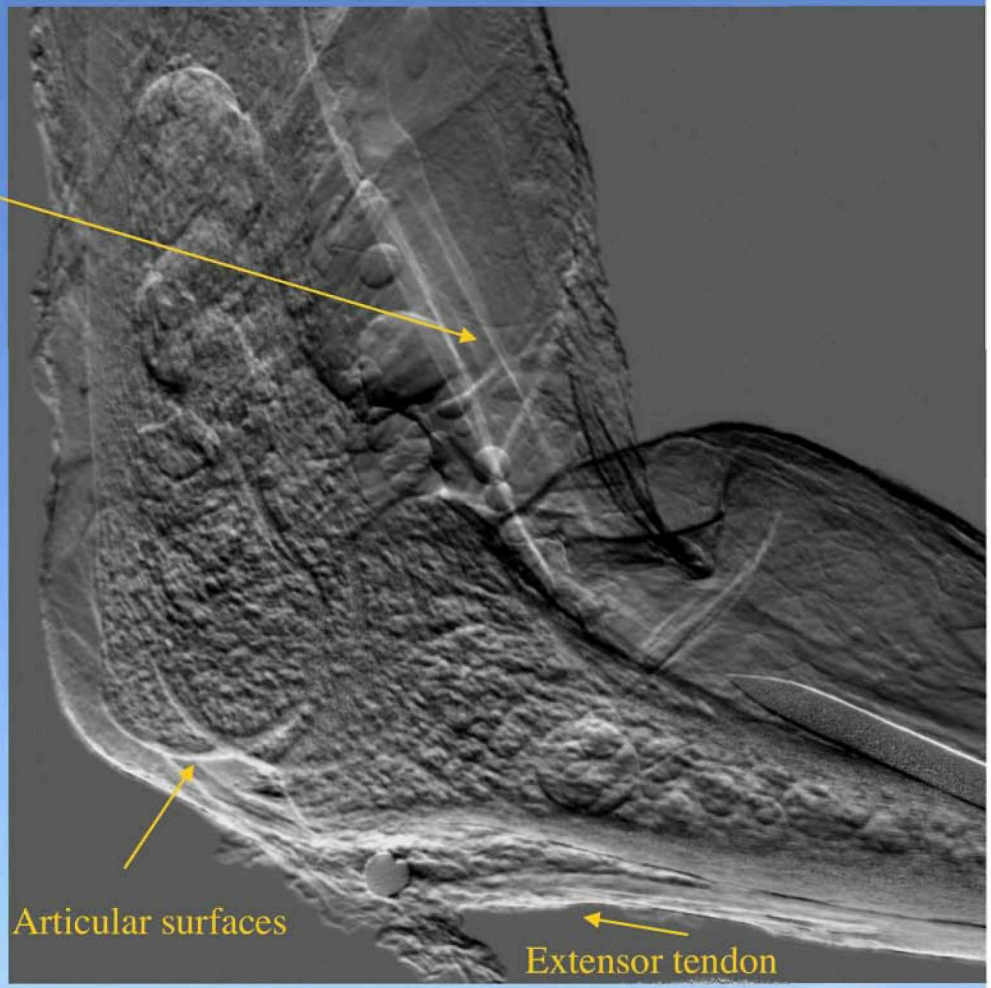
Refraction Image

R. Lewis, C.Hall, R.H.Menk et al.

Index finger proximal interphalangeal joint



Apparent absorption Image



Refraction Image

R. Lewis, C.Hall, R.H.Menk et al.

IV

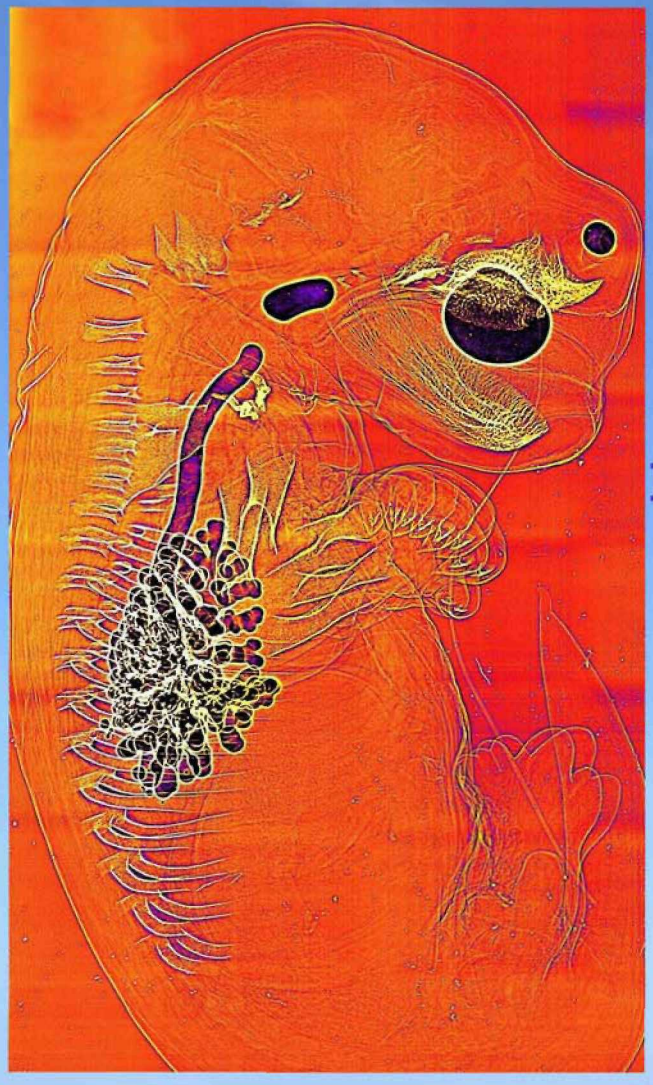
Effects of Ventilation on Lung Liquid Clearance at Birth visualized by PHC

Experience at SPRING-8

Technique:PHC

Image modality: planar

Lung Liquid Clearance at Birth



Aeration of the lung and the transition to air-breathing at birth is fundamental to mammalian life.

It initiates major changes in cardiopulmonary physiology.

The dynamics of this process and the factors involved are largely unknown, because it has not been possible to observe or measure lung aeration on a breath-by-breath basis.

Birth: a major physiological challenge

- Clear the airways of liquid
- Entry of air generates surface tension
- Separation of the pulmonary and systemic circulations
- 10 fold increase in pulmonary blood flow
- Large increase in blood oxygenation

Courtesy of Marcus Kitchen, School of Physics

Lung Aeration in Preterm infants:

Can suffer from:

- Airway liquid retention → respiratory insufficiency
- Non-uniform ventilation → lung injury
- Delayed/blunted physiological transformation

It has not been possible to observe or measure lung aeration

- Enter Phase Contrast X-ray Imaging!

Imaging lung aeration from birth

- Animal model: rabbit pups
- Imaged pups with PHC at SPring-8, Japan (Beamline 20B2).
  - Either before the first breath (fetus) or at fixed intervals after birth (up to 2h)

Courtesy of Marcus Kitchen, School of Physics

MONASH University
Science

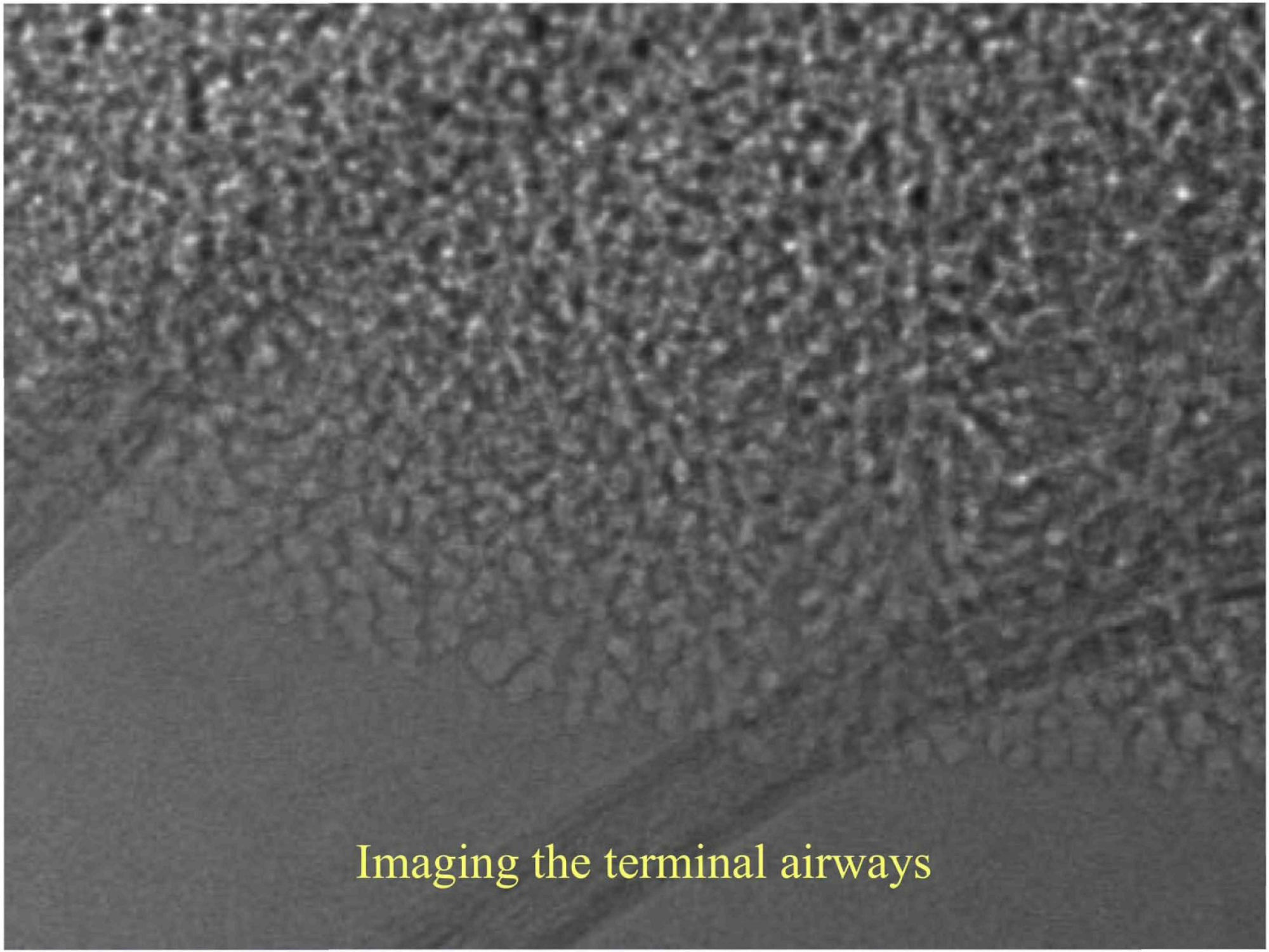
elettra

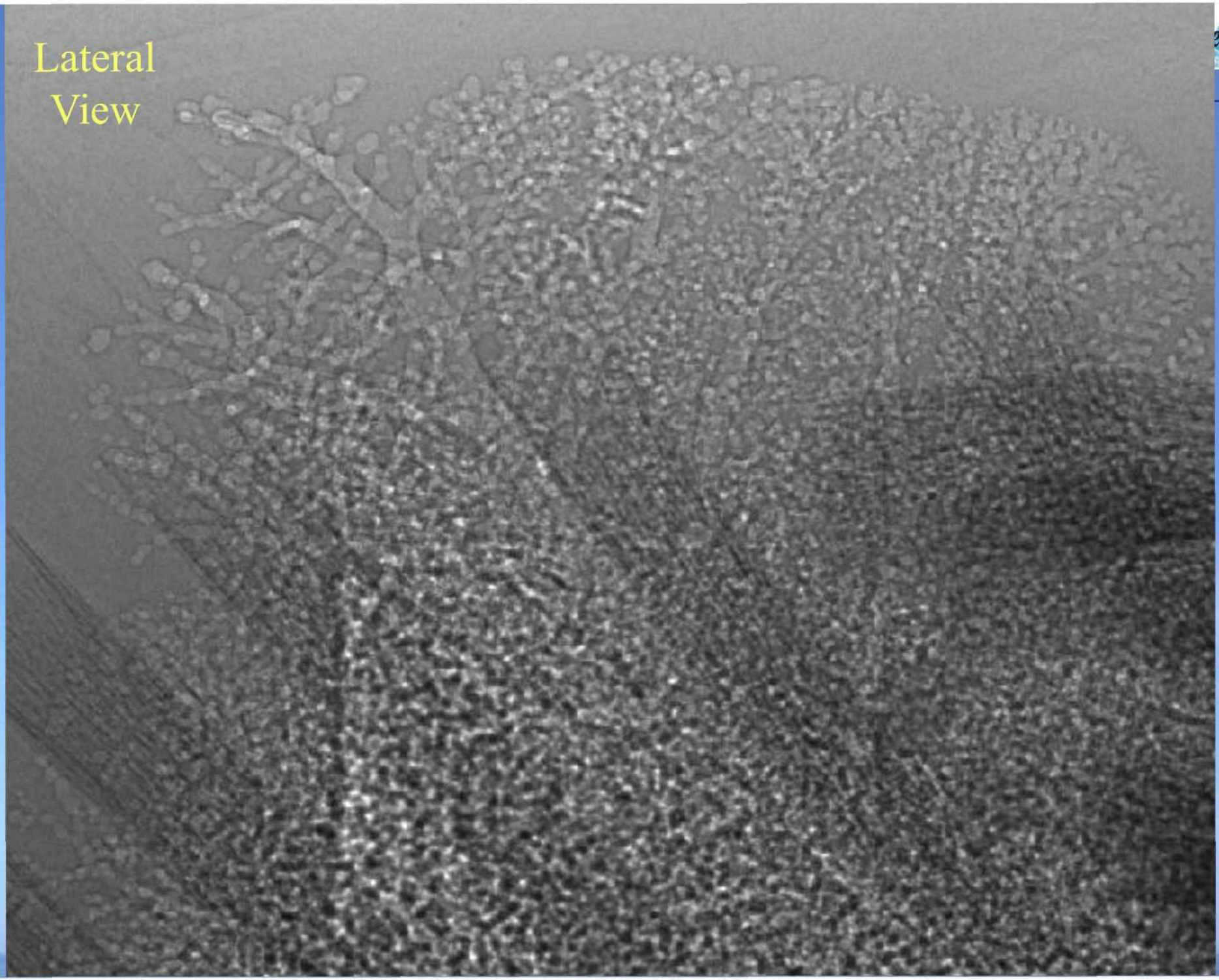
X-ray imaging of the lung

Absorption Contrast

Phase Contrast, 25 keV, z=2 m

Courtesy of Marcus Kitchen, School of Physics


Imaging the terminal airways


Lateral
View

Acknowledgement

to the SYRMEP/SYRMA team:

A.Abrami, V.Chenda, D.Dreossi, L.Mancini, E.Quai, R.H. Menk, N.Sodini, F.Zanini
Sincrotrone Trieste

F.Arfelli, E.Castelli, R.Longo, L.Rigon
University and INFN Trieste

P.Bregant, M.Cova, E.Quaia, D.Sanabor, M.Tonutti, F.Zanconati
Radiology Dept. and Health Physics – University and Cattinara Hospital Trieste

V

Studies of human aortas

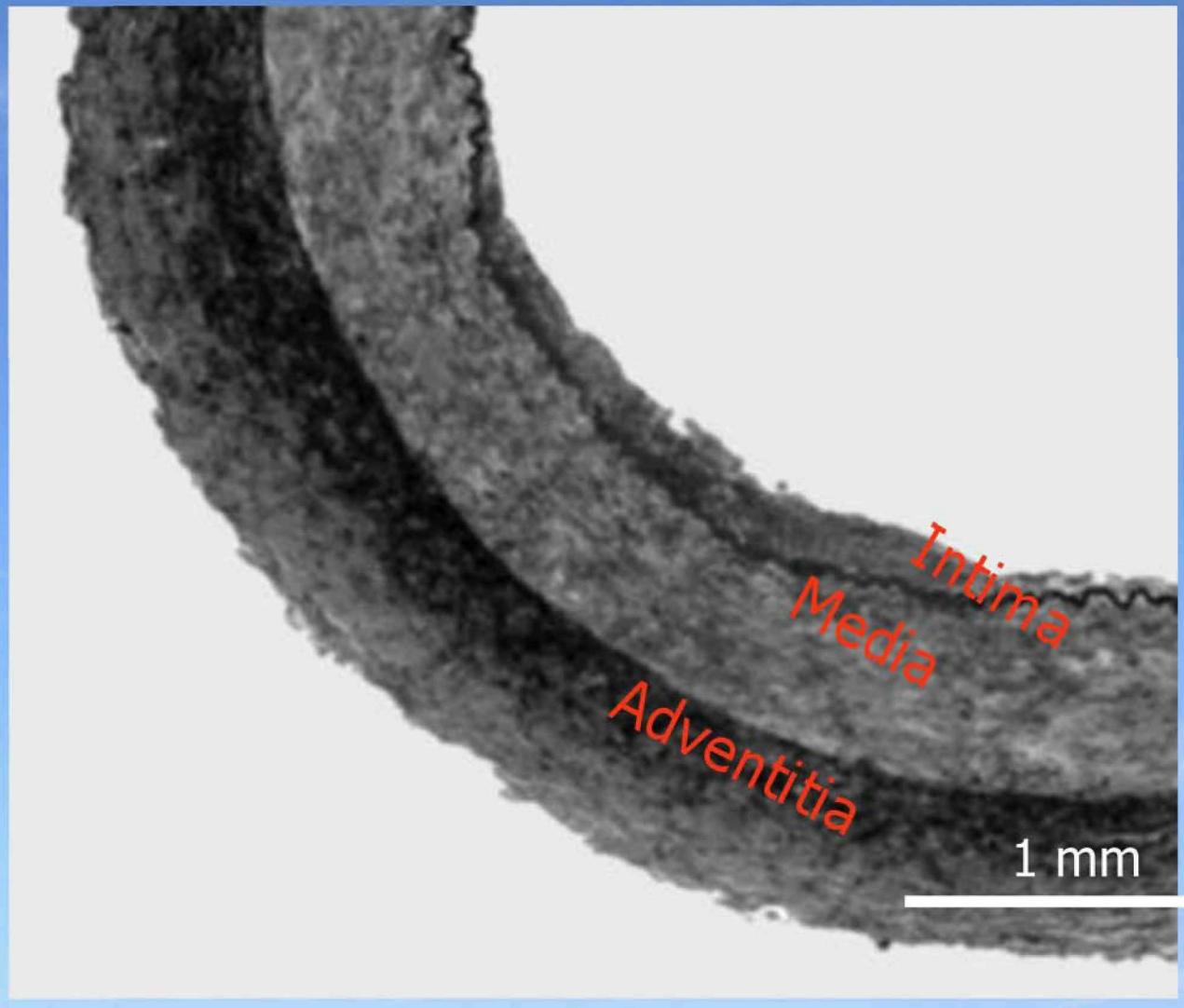
Technique: PHC

Image modality: micro-CT

Micro-tomography of human aortas

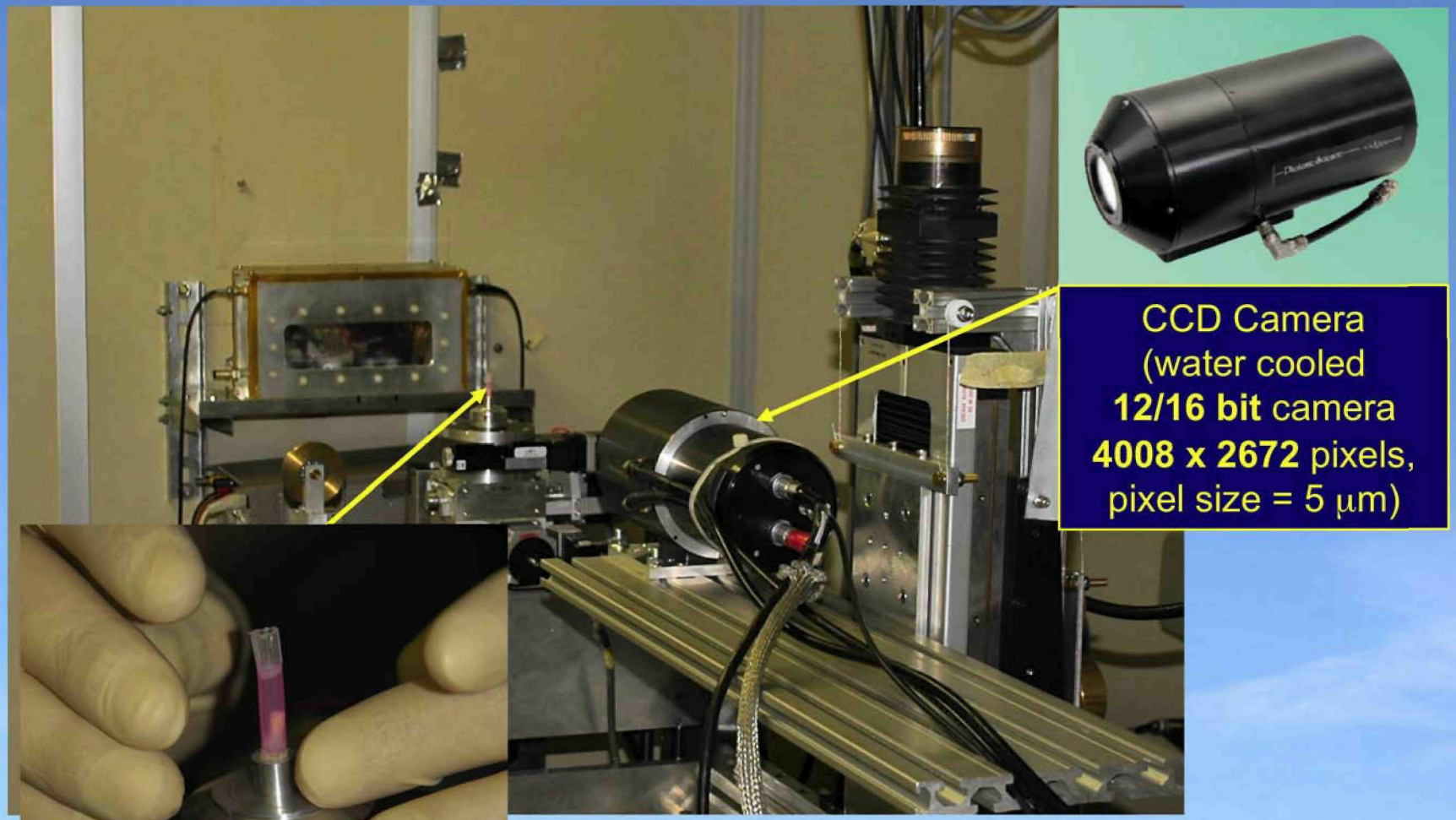
In situ characterization of aterosclerotic plaques

- The investigation of the arterial wall is an essential issue for the early diagnosis of aterosclerosis
- Aim of the feasibility study at SYRMEP: reveal the different layers and plaques components of diseased arteries.
- Final aim: generate morphological models for finite element analysis codes applied for stress-strain analysis of artheries. Bio-mechanical properties are studied by SAXS. These codes allow to simulate artherial walls behavior during medical interventions such as balloon angioplasty.
- At present hrMR images are used but tissue differentiation is poor. Can we improve it using SR?



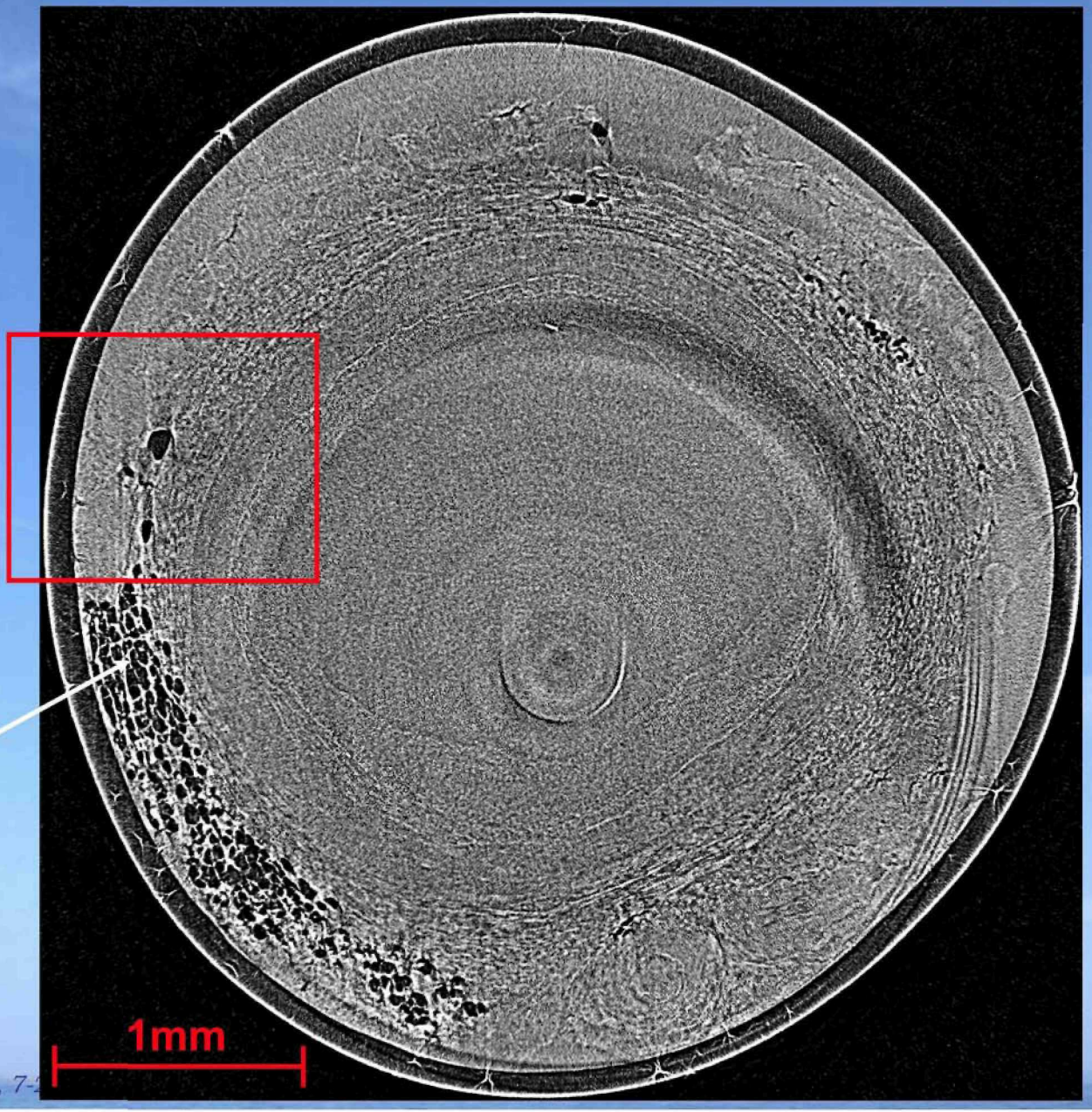
Cross section of a human artery

SYRMEP: Micro-tomography set-up



Aged non-diseased coronary vessel

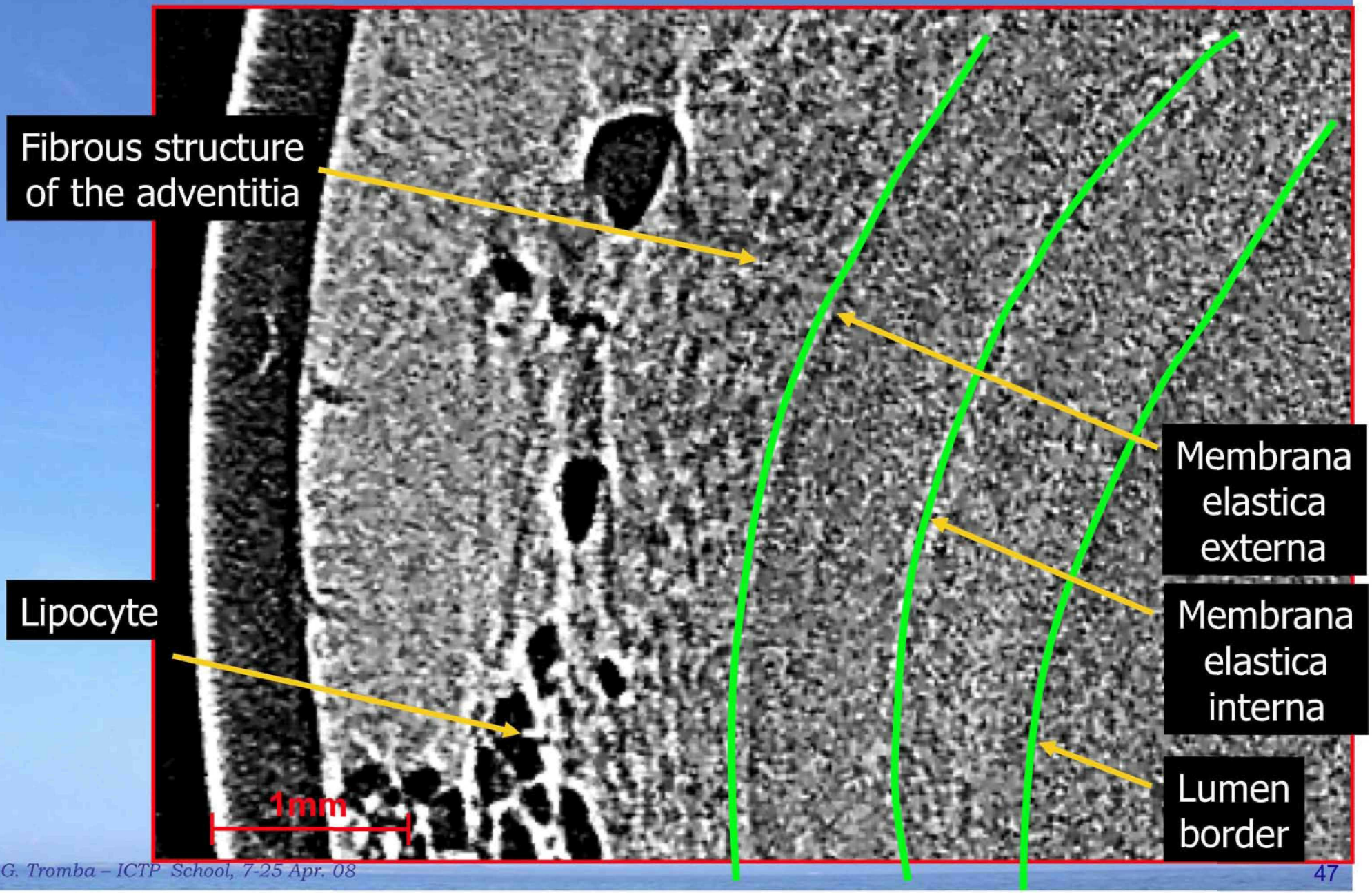
Slice



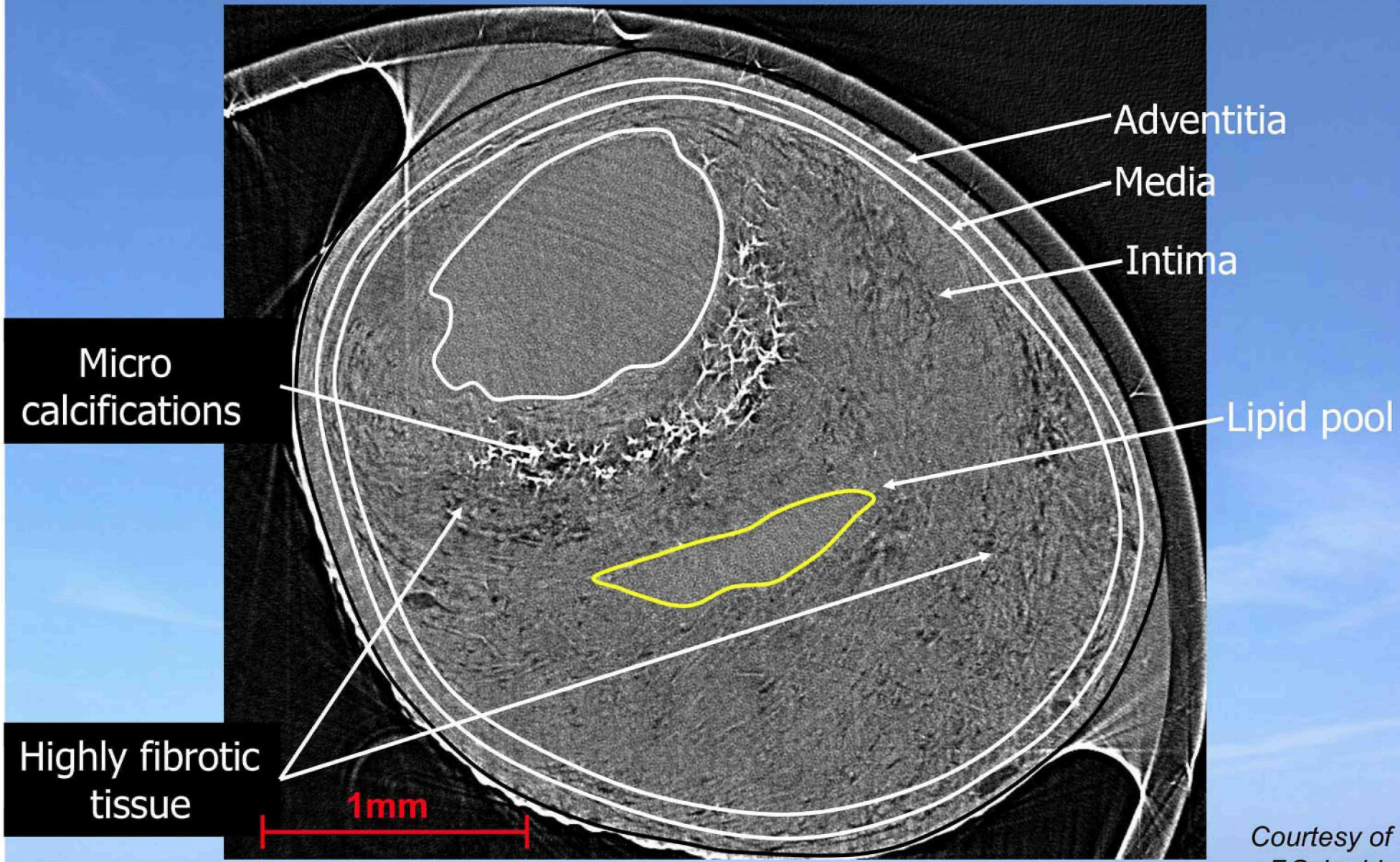
Lipocytes
(fat cells)

Courtesy of F.Schmid

Aged non-diseased coronary vessel

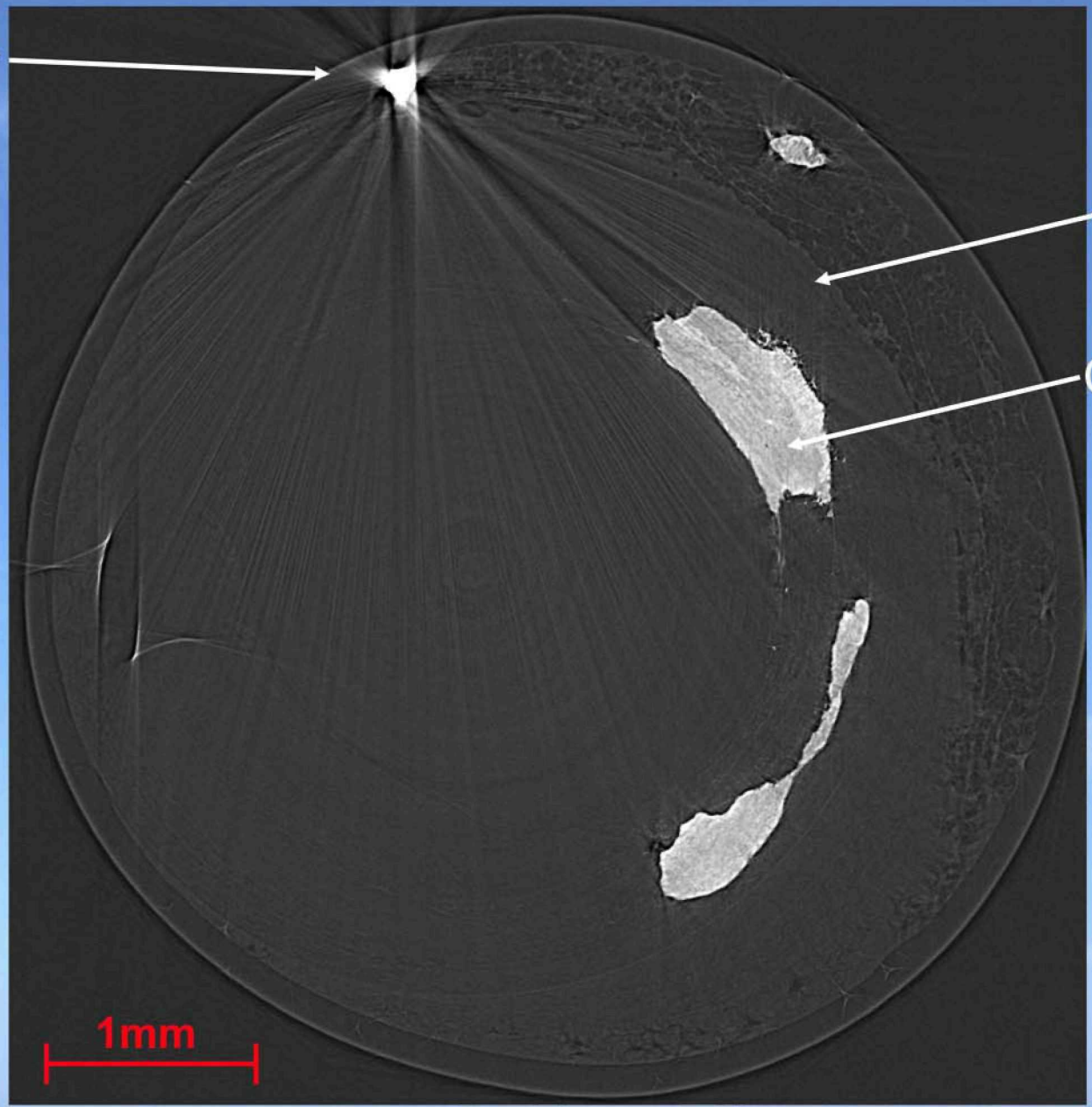


Aged diseased coronary vessel



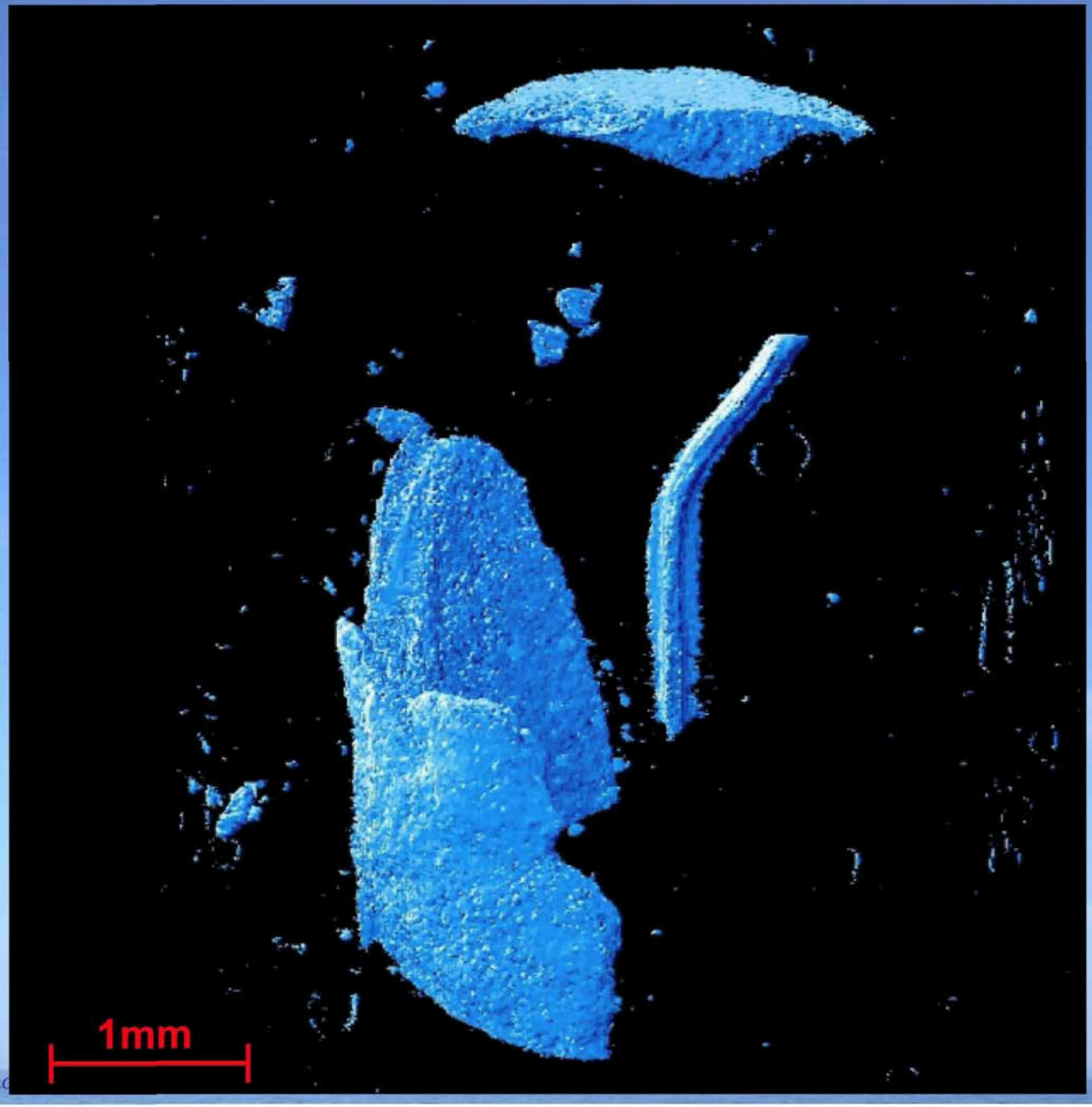
Courtesy of F.Schmid

Calcified coronary vessel



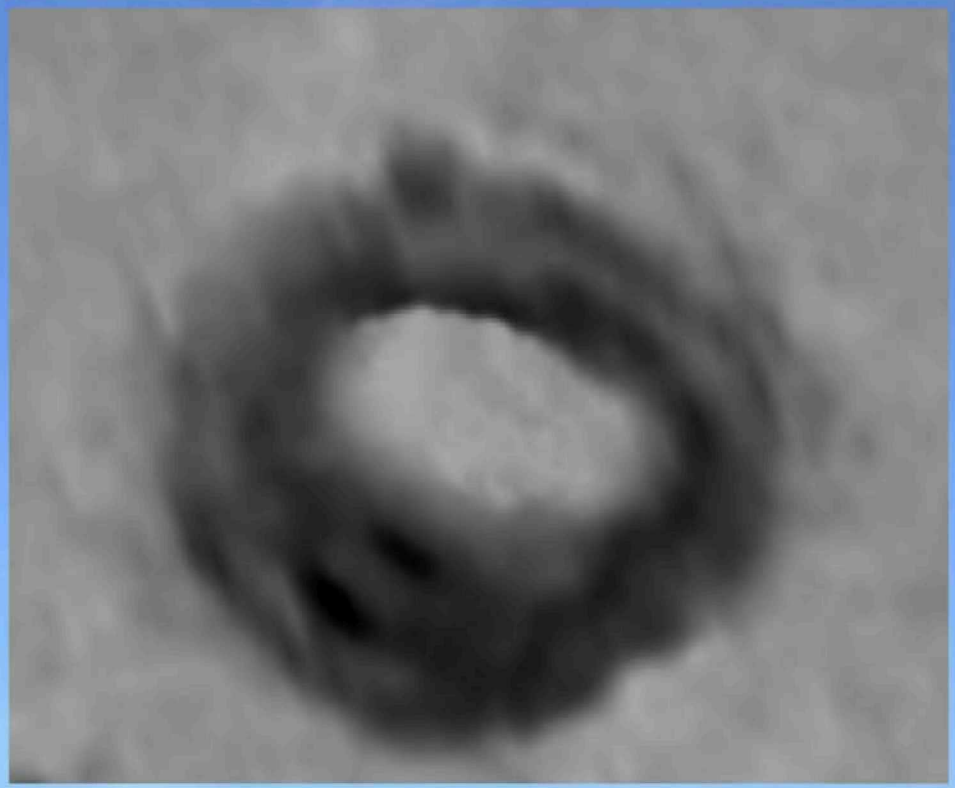
Courtesy of F.Schmid

3D-Reconstruction of the calcification

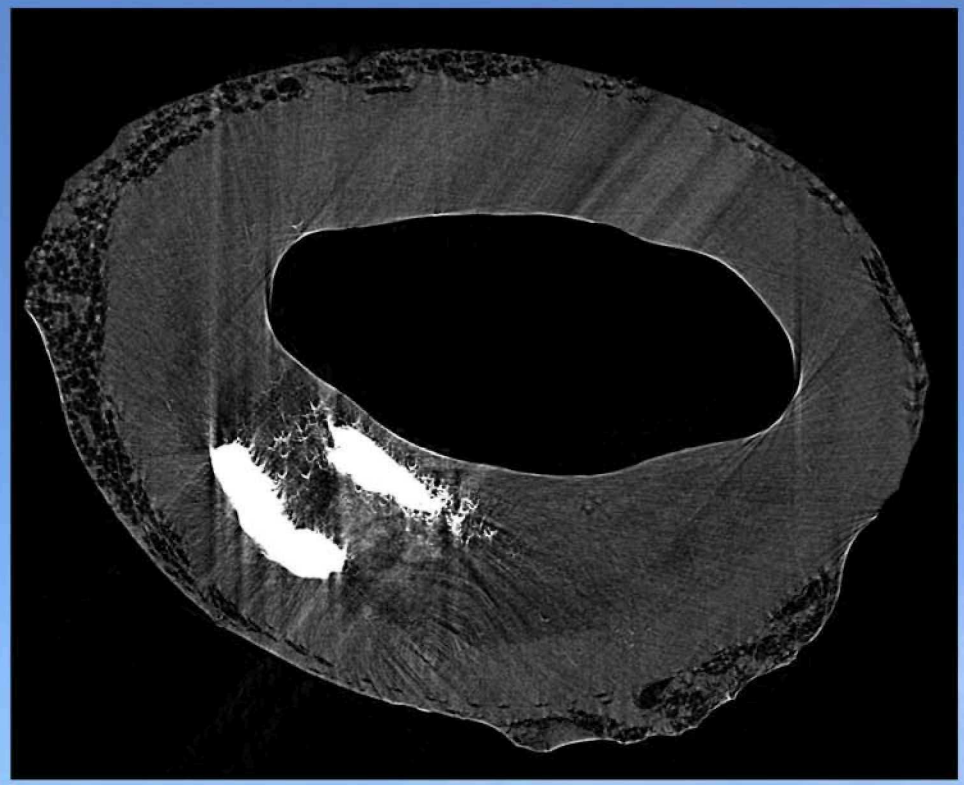


Courtesy of F.Schmid

Comparison Between MR Imaging and μ-CT



MR image
100x100x400μm



SR image (phase contrast)
12x12x12μm

Courtesy of F.Schmid

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