Imaging and Radiotherapy with Synchrotron X-rays

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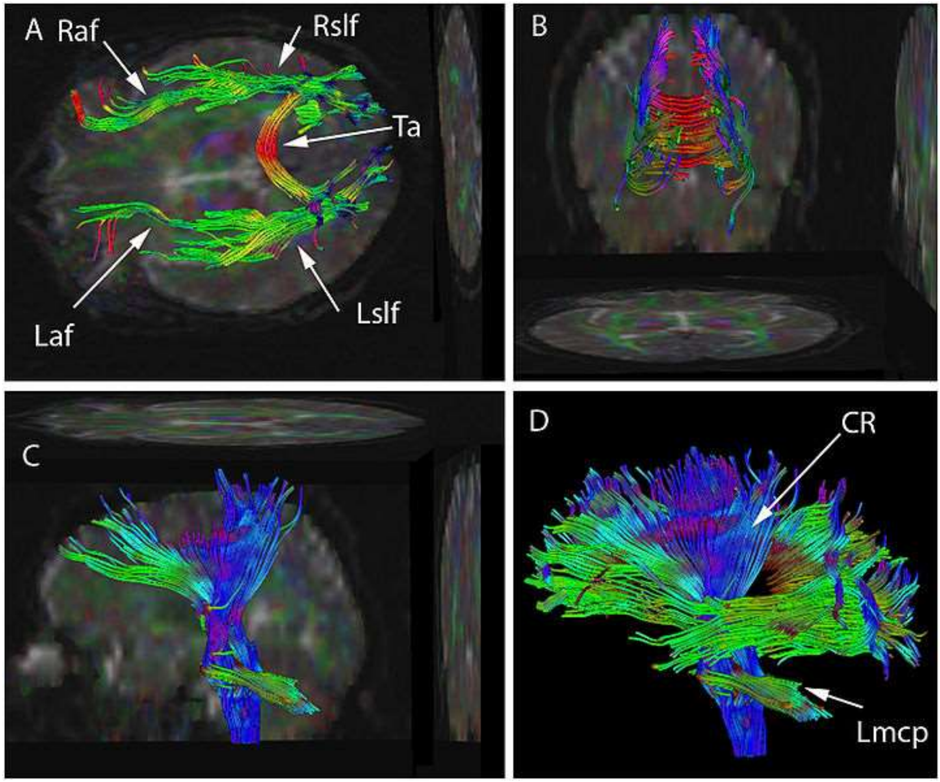
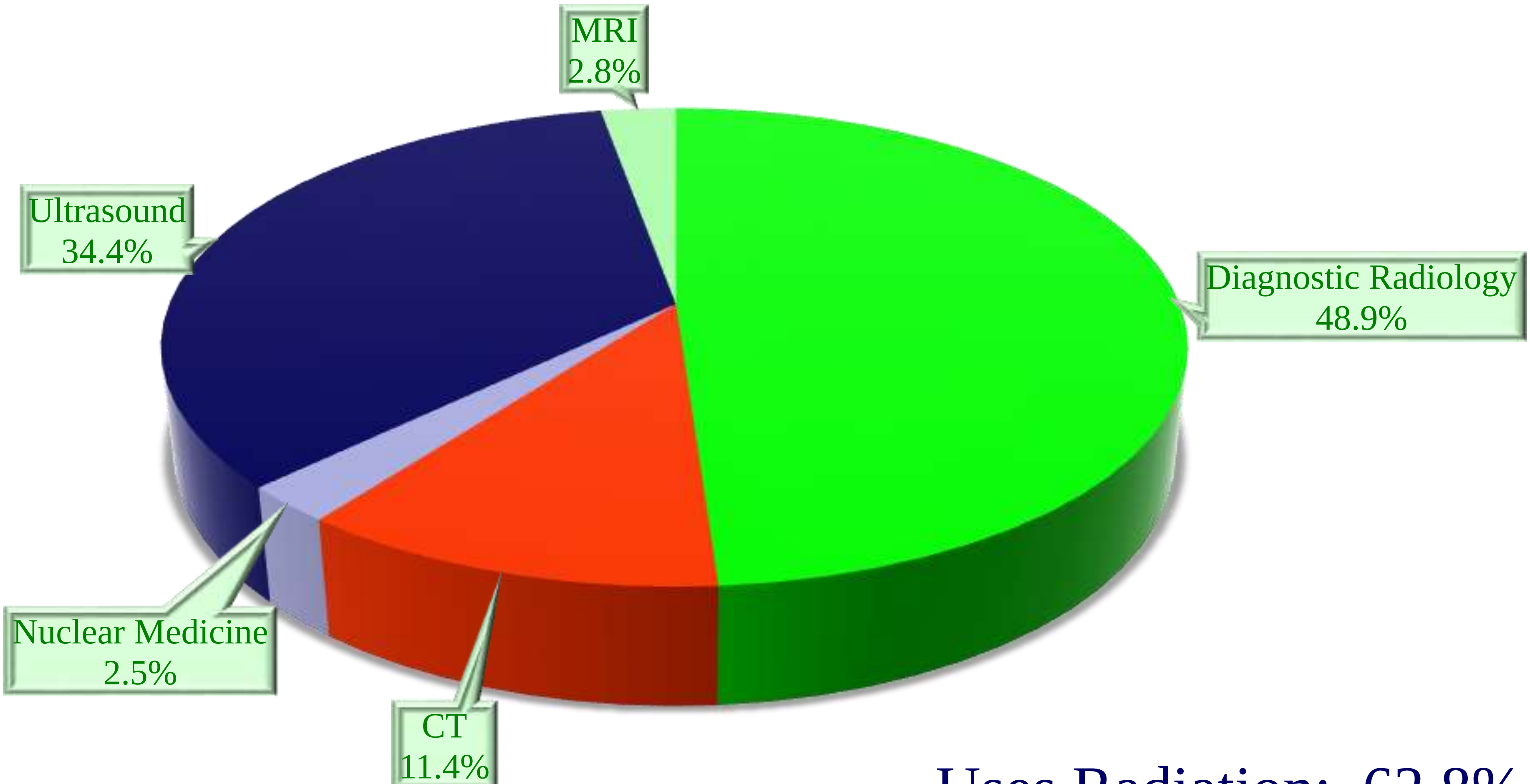
Other Modalities

- Ultrasound
  - ✓ Cheap
  - ✓ No radiation dose
  - ✗ Cannot penetrate bone or air
  - ✗ Spatial resolution degrades with depth
  - ✗ Scan times are minutes
- MRI
  - ✓ Fantastic soft tissue contrast
  - ✓ Minimal radiation dose
  - ✗ Expensive
  - ✗ Scan times are many minutes
  - ✗ Spatial resolution f(B)

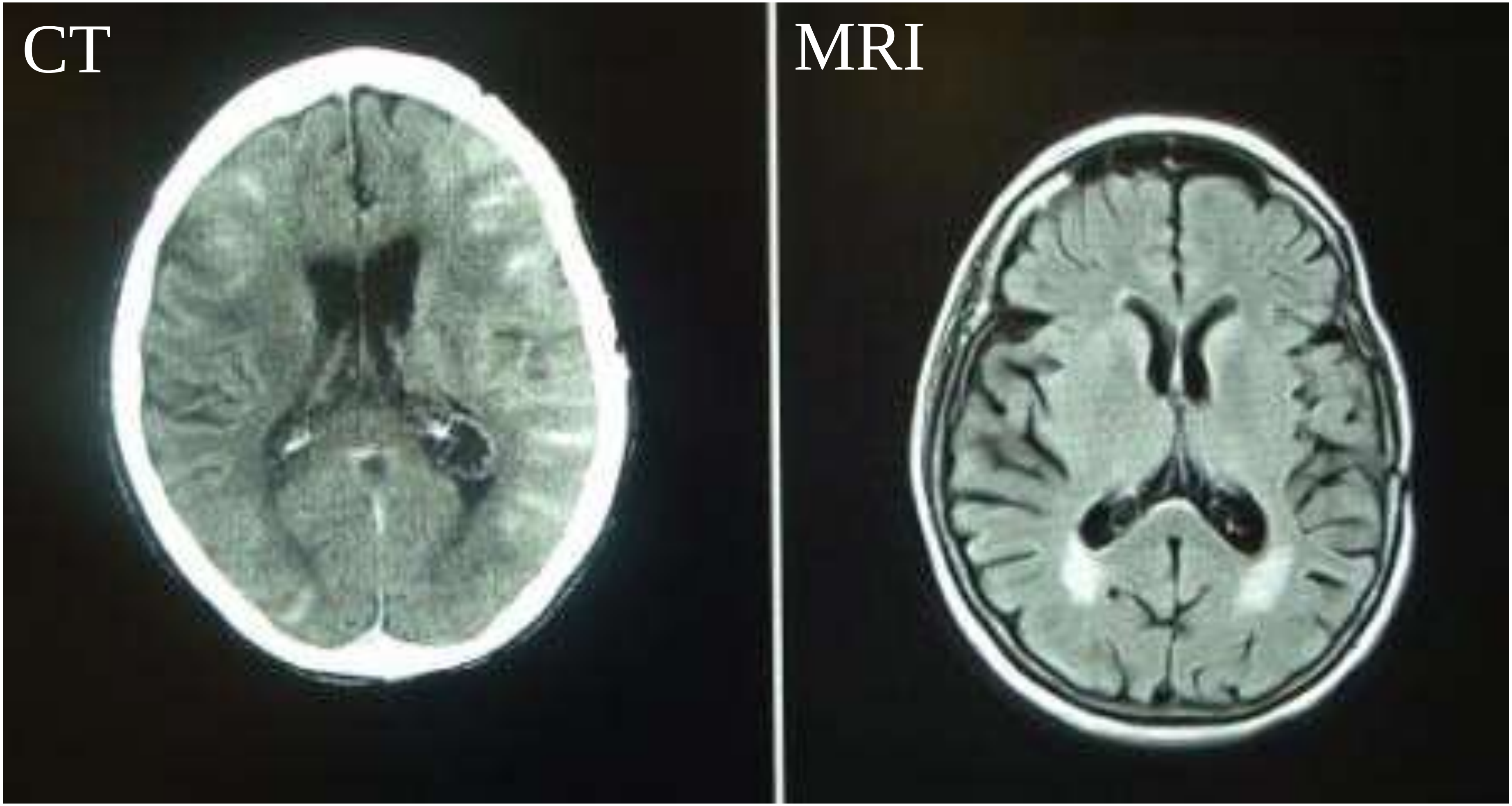


Diagnostic Imaging in Australia



Uses Radiation: 62.8%
X-ray & CT: 60.3%

MRI-CT Comparison



- MRI not always best contrast

MRI

- Fabulous Images but
- Cost:
  - **CT:** From $700 to $2,200
  - **MRI:** From $1200 to $4000
- Time taken for scan:
  - **CT:** Usually completed within 5 minutes
  - **MRI:** Typically 30-40 minutes
- Narrow tunnel and noisy
- Metal implants and pacemakers contraindicated

MRI Accidents

Current Trends

- Preventative medicine is a good idea
- Medical imaging procedures can detect disease at a stage when it can be treated effectively
  - Funding bodies (public and private) will fund imaging procedures
- There is a trend towards more imaging, particularly screening
  - Mammography
  - Whole body CT scans
- Screening means go fast!

e lumen, very sharp

SIEMENS

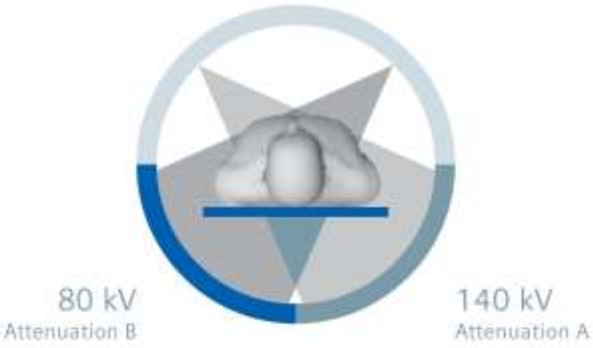
SOMATOM Definition Flash

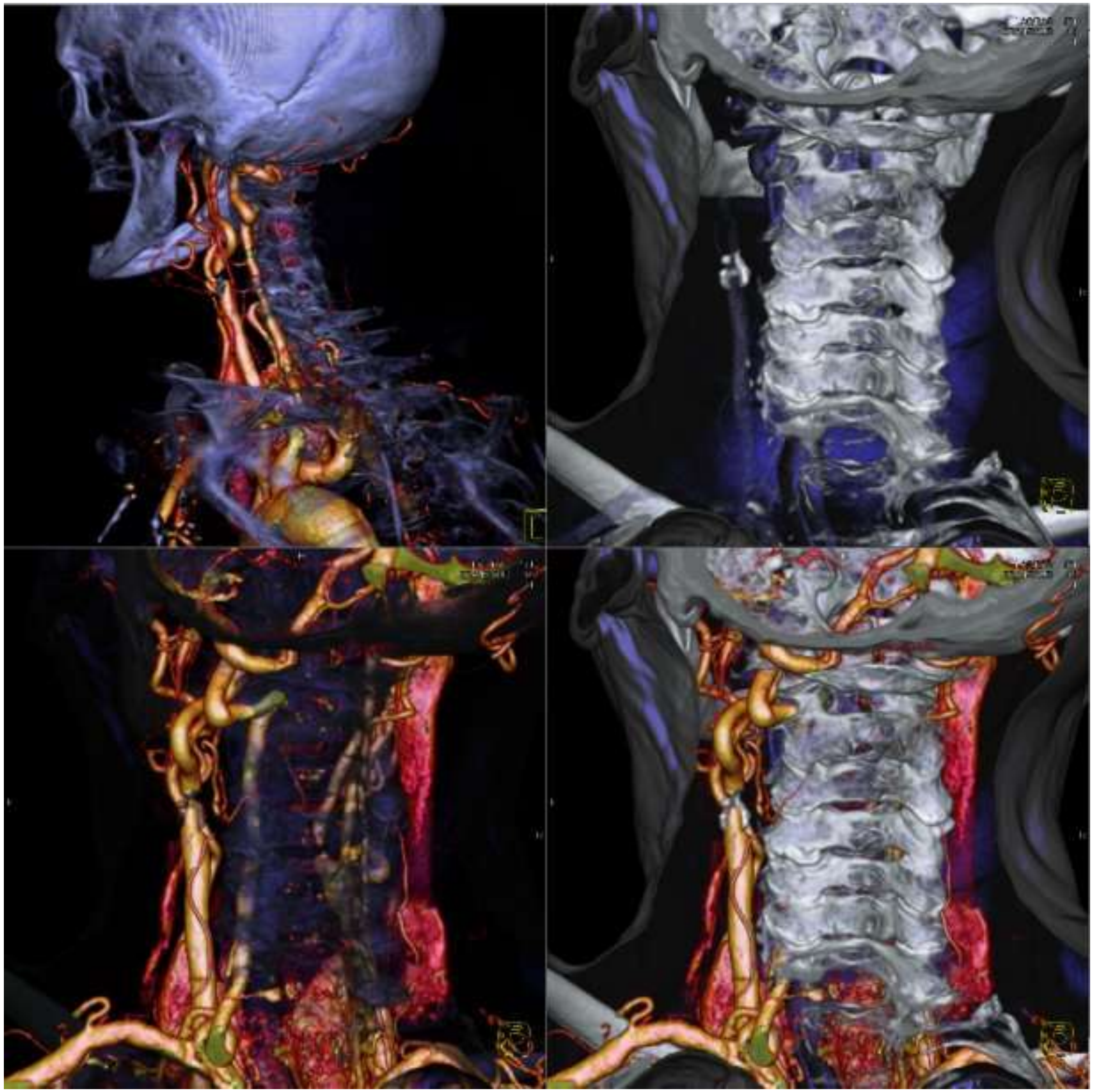
Flash speed.
Lowest dose.

collimation: 128 x 0.6 mm
spatial resolution: 0.33 mm
scan time: 2.3 s
scan length: 613 mm
rotation time: 0.28 s
100kV, 183 effective mAs
6.2 mSv

Courtesy of Centre Cardio-Thoracique de Monaco / Monaco

Dual Energy CT





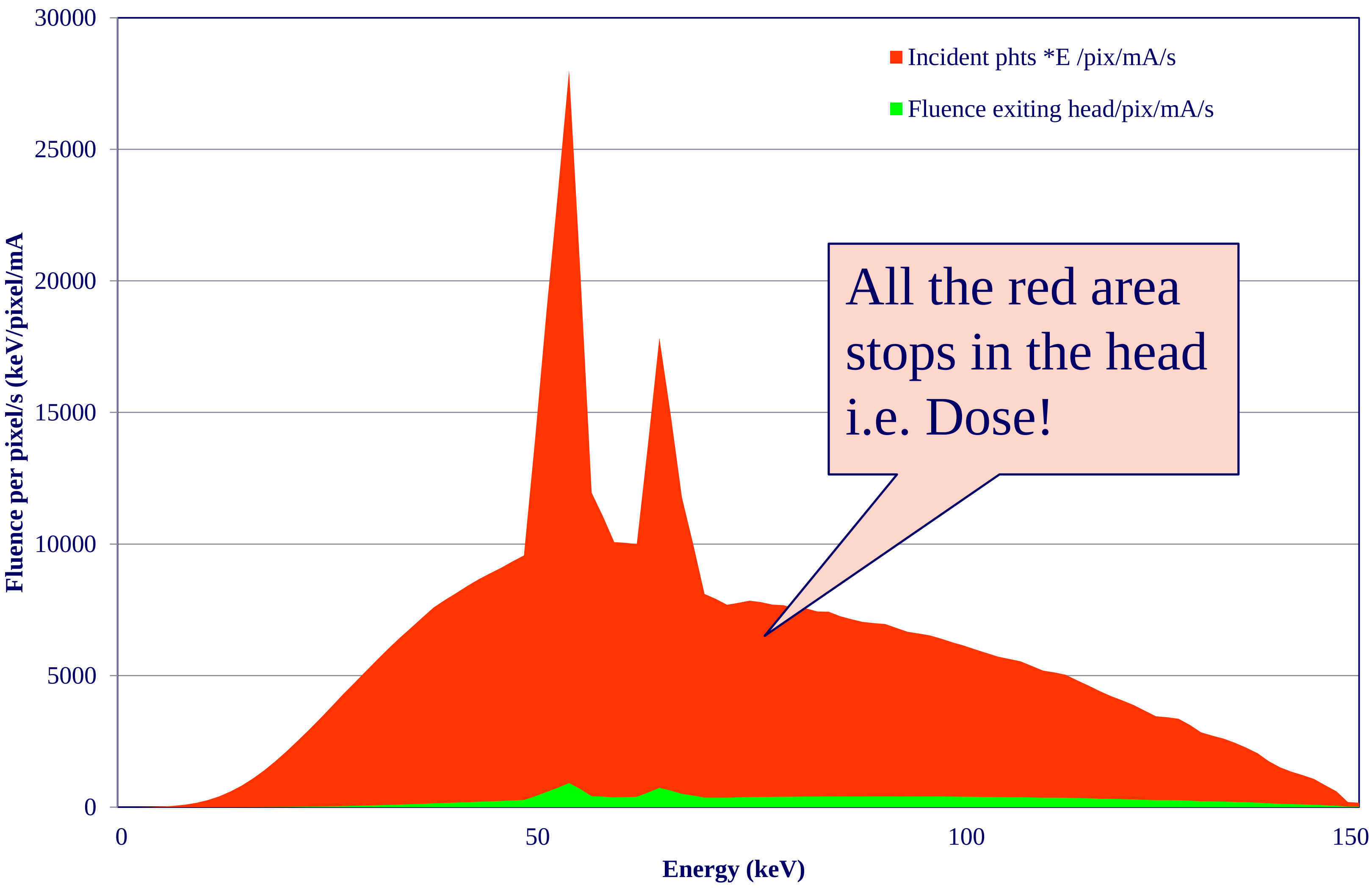
Plaque in Carotid

- 9 s for 348 mm
- Spatial Res. 0.33
- Rotation 0.33 s
- 140/80 kV
- 60/230 mAs (eff.)

Imaging Using Ionising Radiation

- Will be here for a long time because it;
- Can perform very fast scans
- Can tolerate implants
- Is relatively cheap
- So what is the risk from all this radiation?

Fluence and Dose: Head



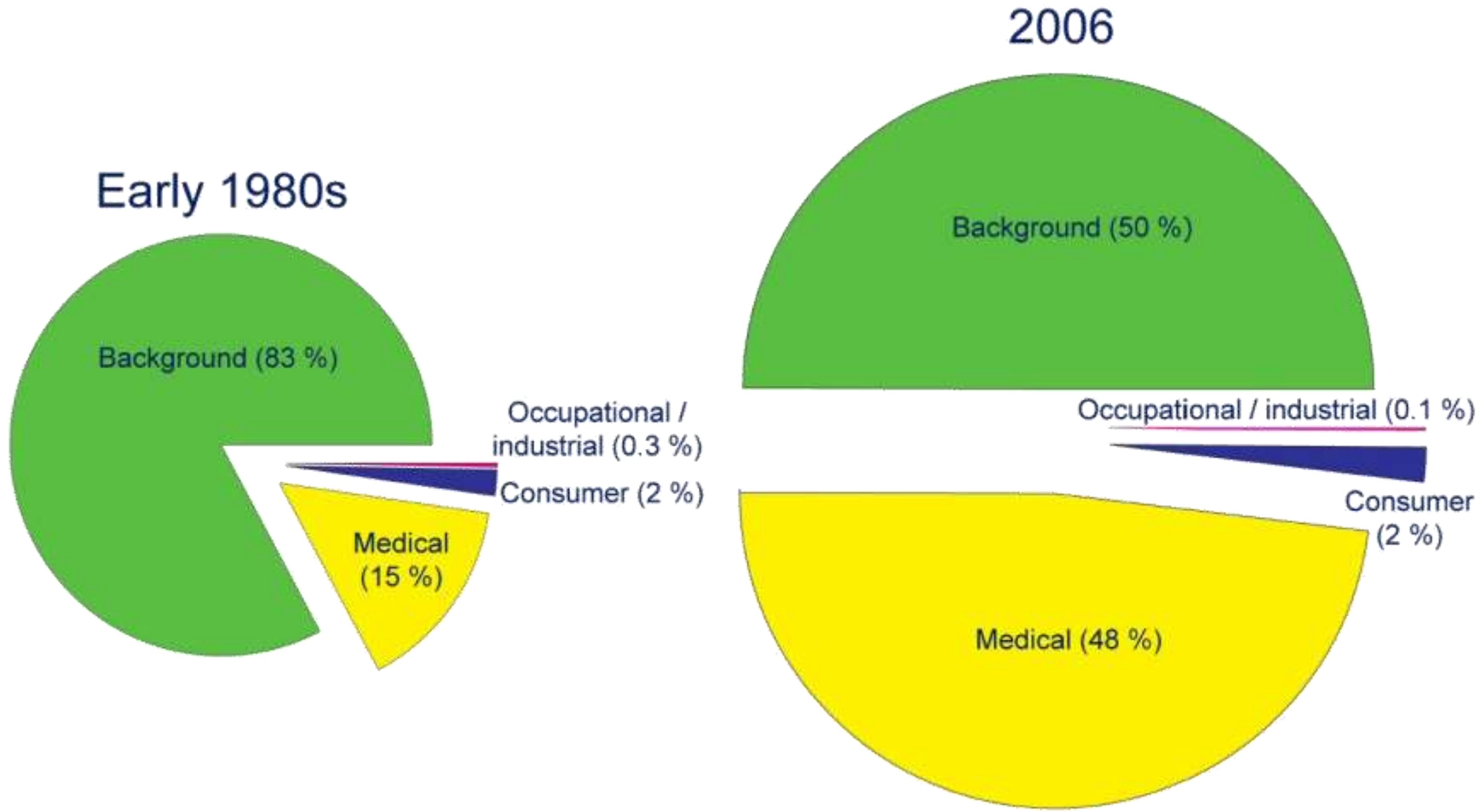
What is the Risk from Radiation?

- A lifetime dose of 100mSv increases cancer risk by ~1%
  - 1000 chest x-rays
  - 100 mammograms
  - 50 head CT scans
  - 10 abdominal or pelvic CT scans
- Background Dose is ~ 2.4mSv/year

- 11 March 2011, Tsunami hits Fukushima. Radiation ~210mSv/yr
- On 31 May, 2011 Fukushima prefecture dose rate was 13mSv/yr
  - 7.5 years to reach 100mSv

- It takes most radiation-induced cancers 10 to 20 years to develop in adults
- The average lifetime risk of developing cancer from all causes is 42%
- From early 1980s to 2006, 7× increase in population dose from medical procedures

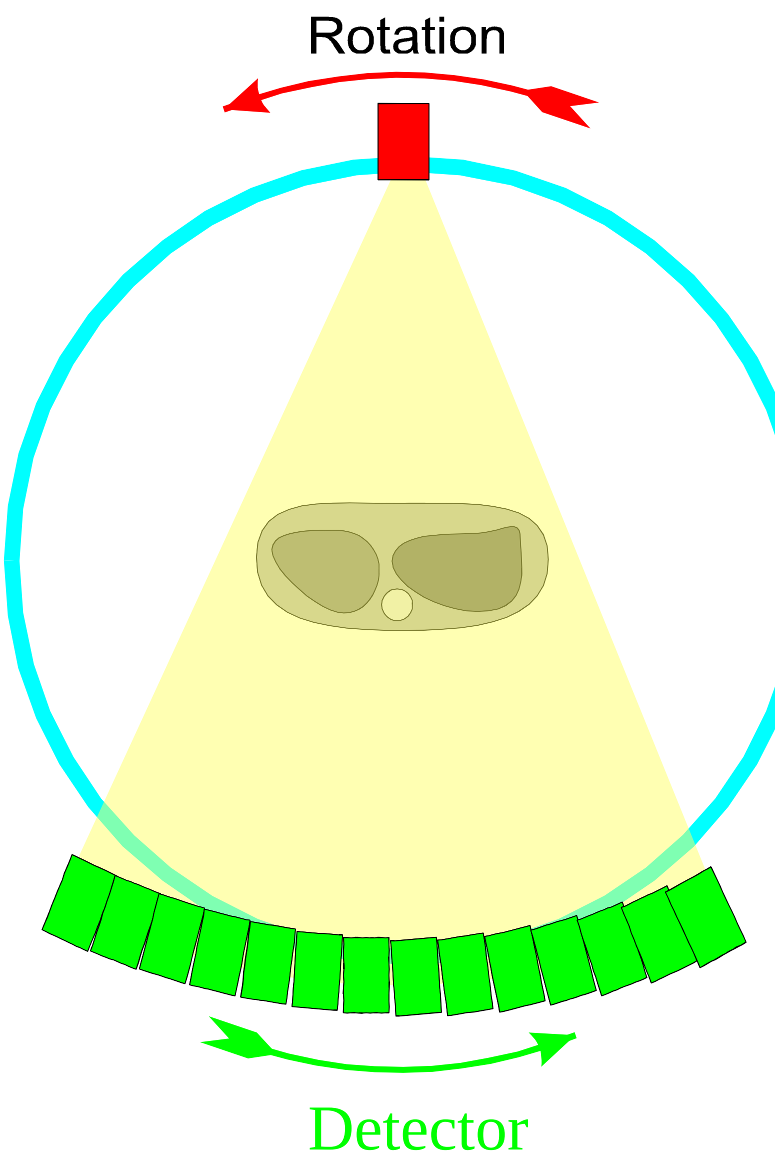
Trends in Radiation Dose from Medical Imaging



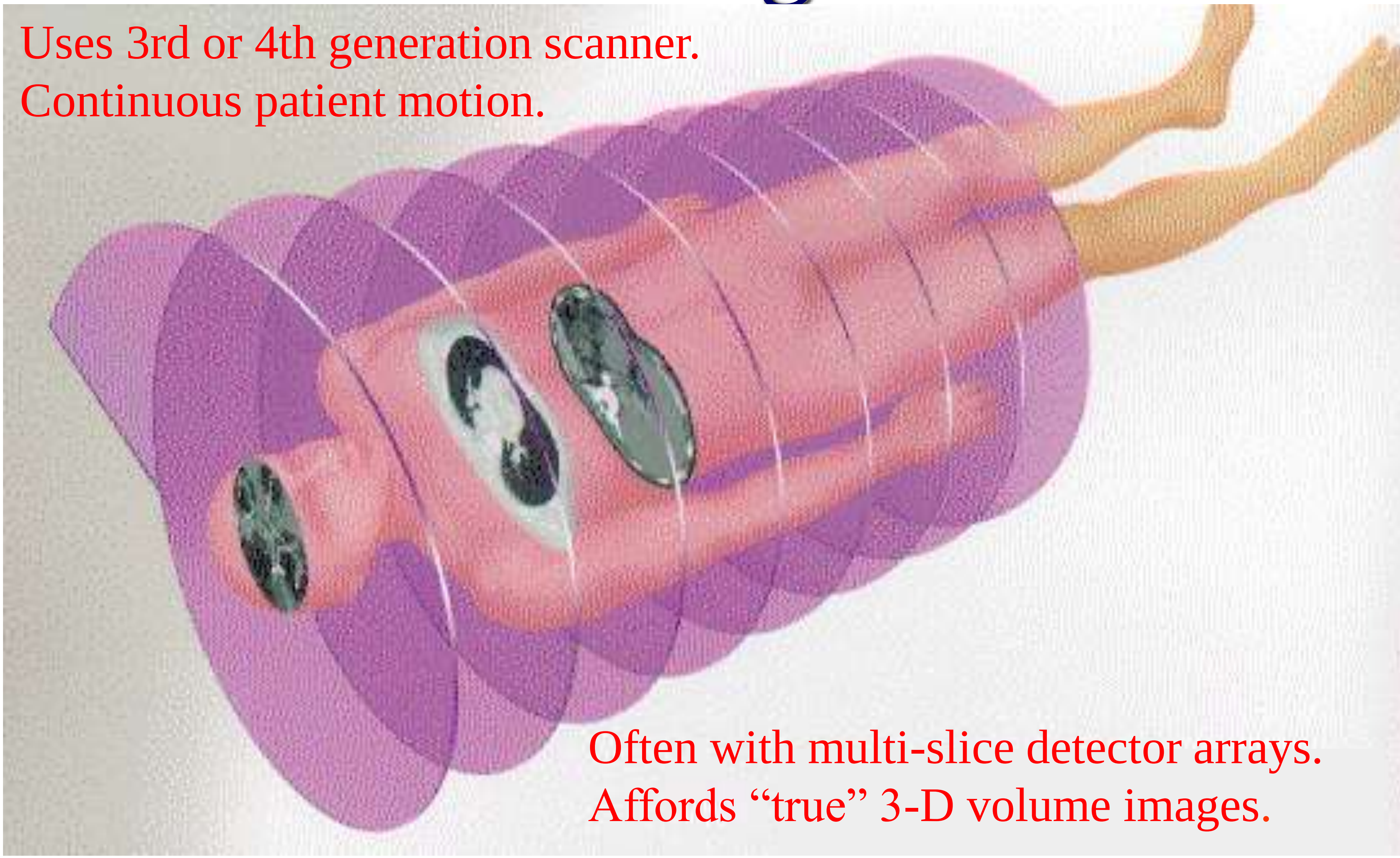
	Early 1980s	2006
Collective effective dose (person-Sv)	835,000	1,870,000
Effective dose per individual in the U.S. population (mSv)	3.6	6.2

3rd Generation CT Scanner

- Multiple detectors
- Translation-rotation
- Large fan beam
- Patient stationary for each 2-D slice acquisition; about 0.1 seconds per slice
- kV = 120, mA = 500
- Image then reconstructed in about 0.1 seconds



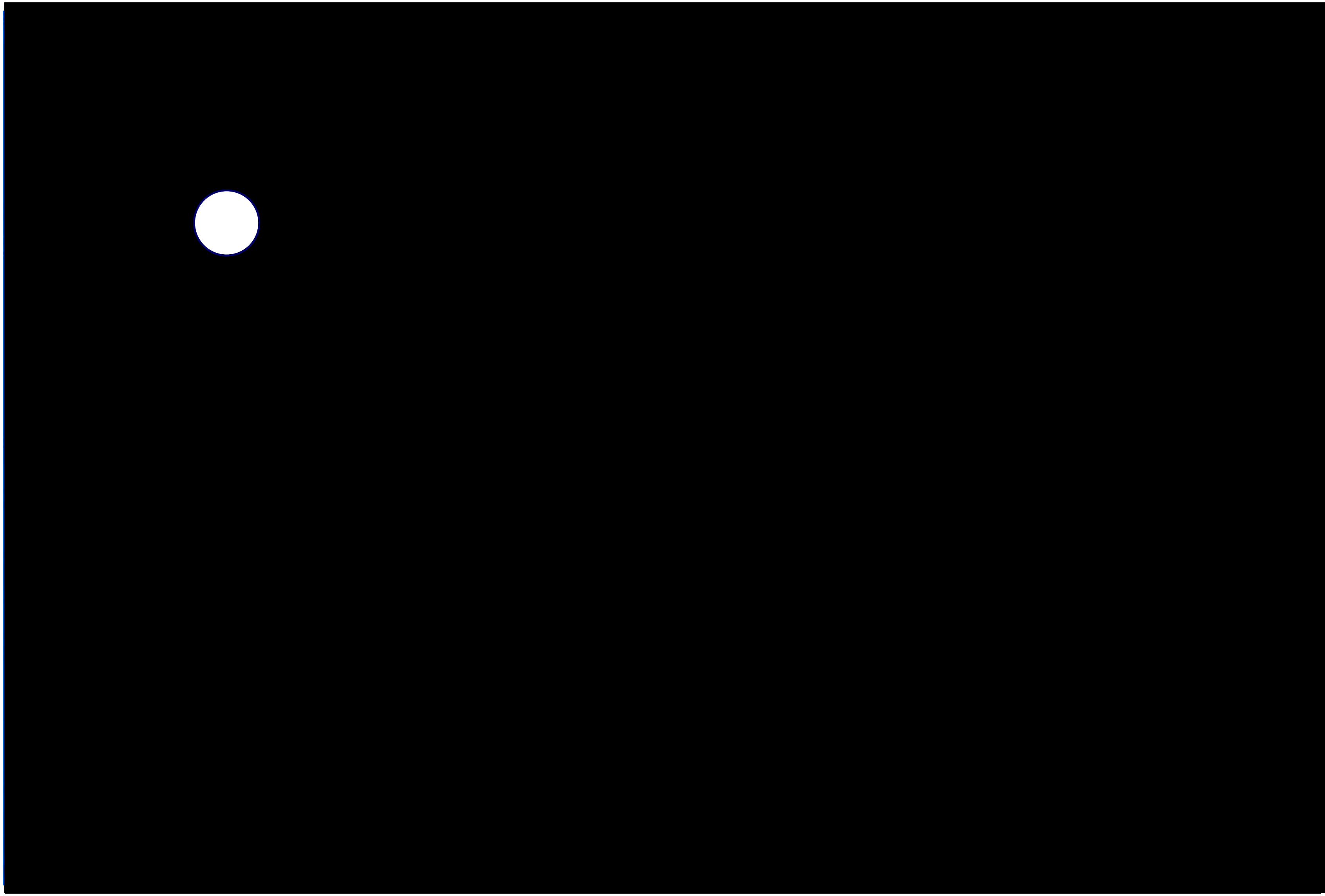
Volume CT image



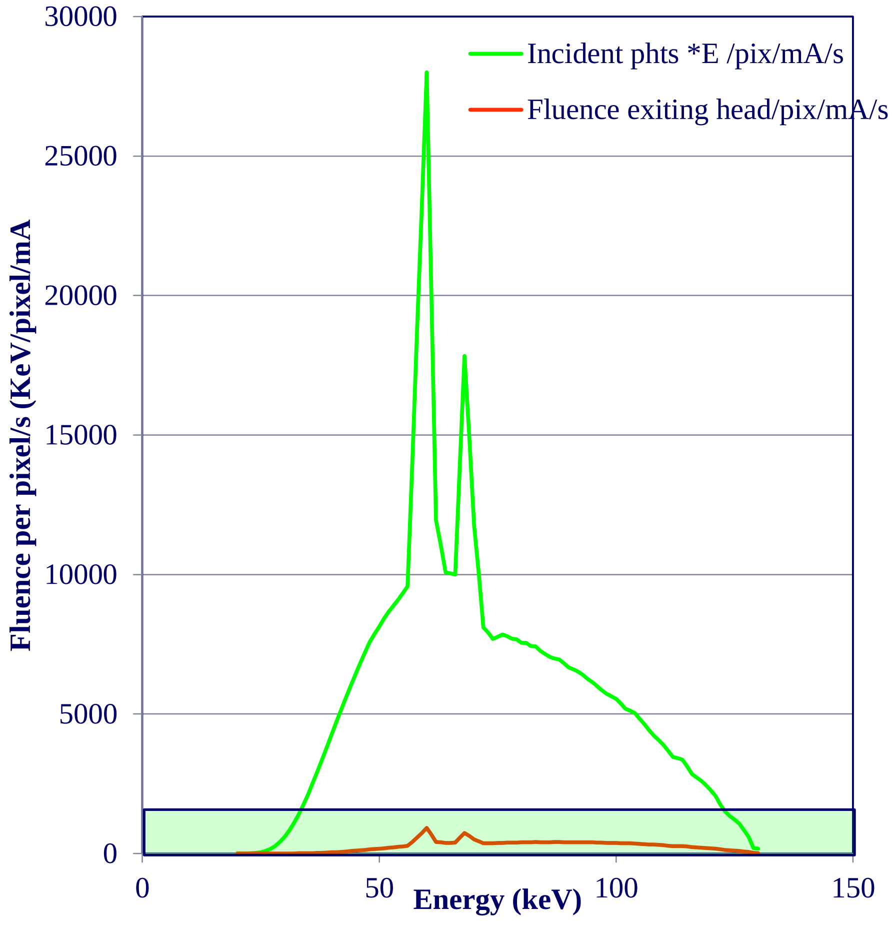
Uses 3rd or 4th generation scanner.
Continuous patient motion.

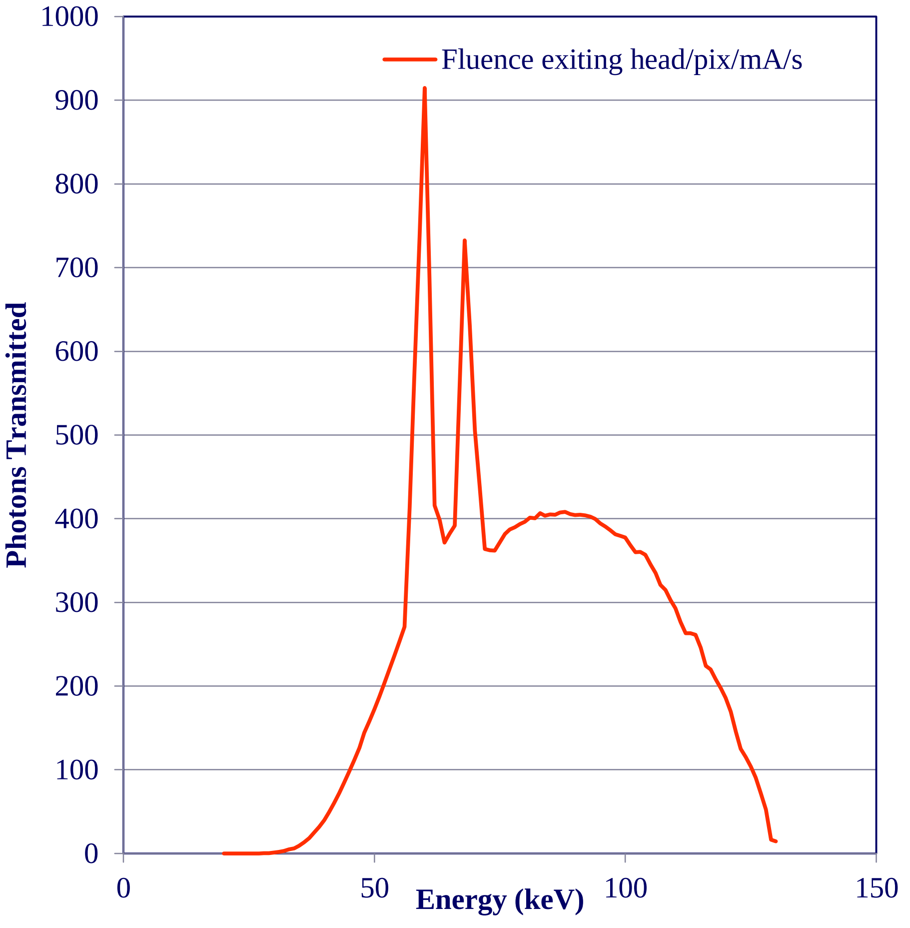
Often with multi-slice detector arrays.
Affords “true” 3-D volume images.

Back Projection in Practice



Beam Hardening

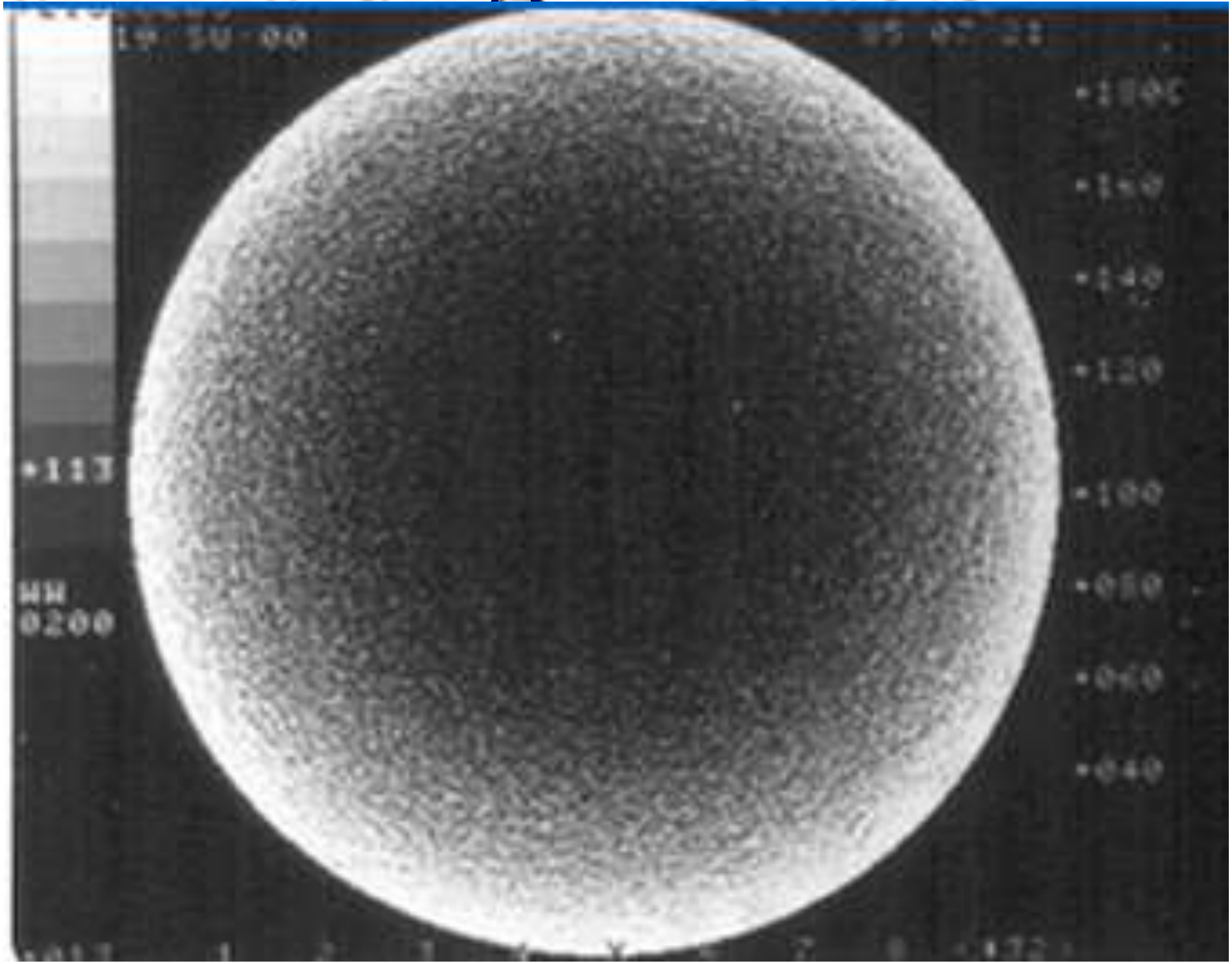




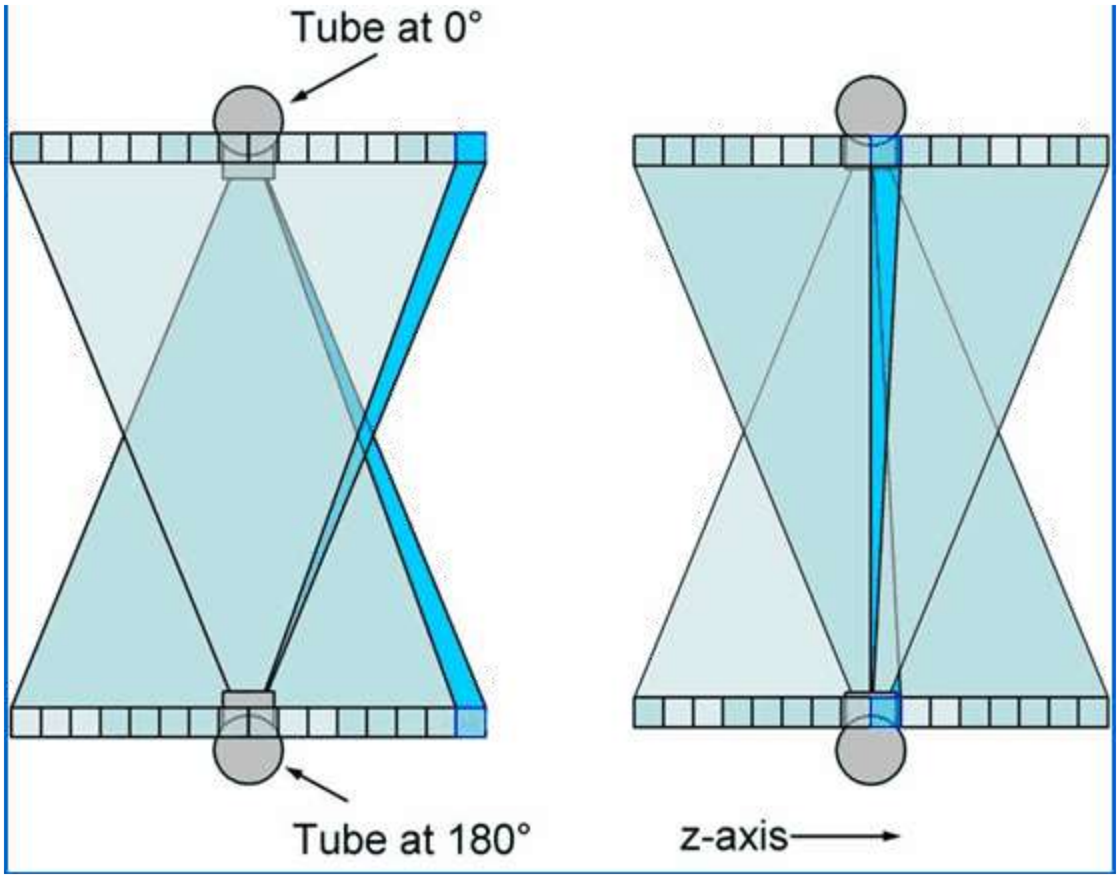
UNIVERSITY OF SASKATCHEWAN MONASH University

Beam Harding Artefacts

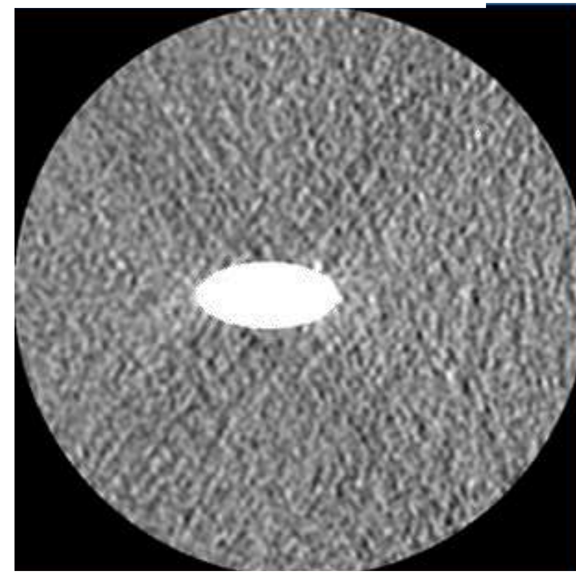
uniform



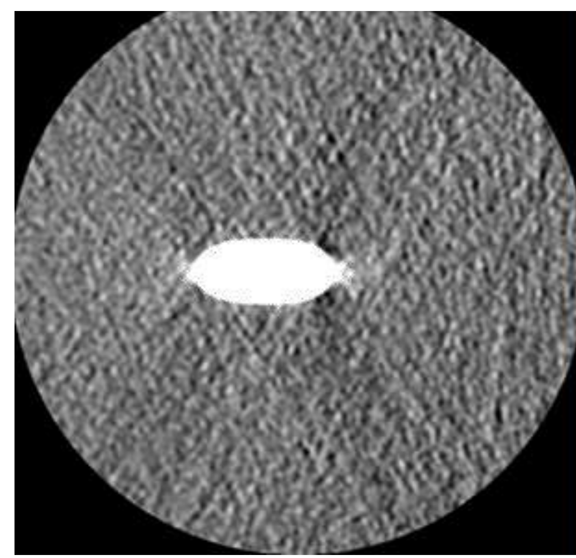
Cone Beam Artefacts



Inner detector row image



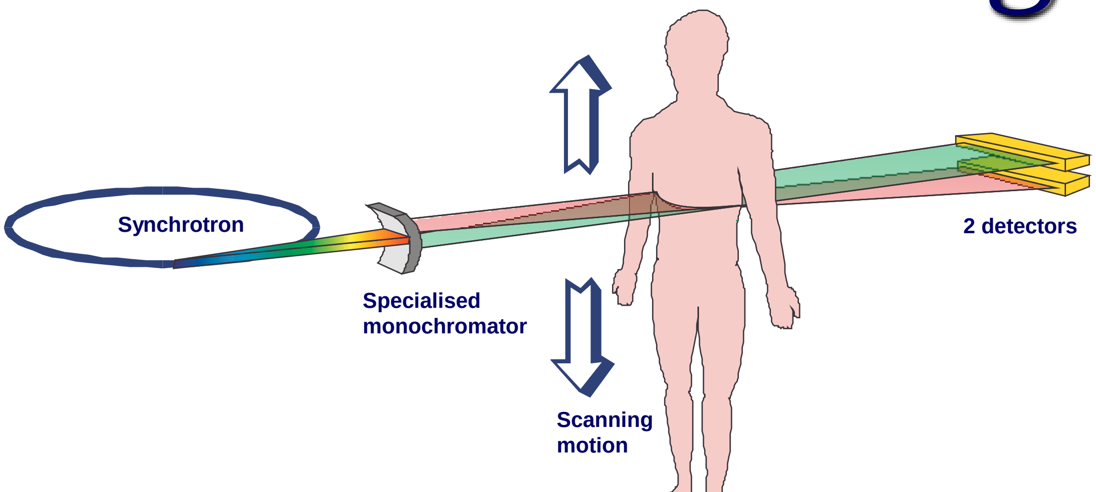
Outer detector row image

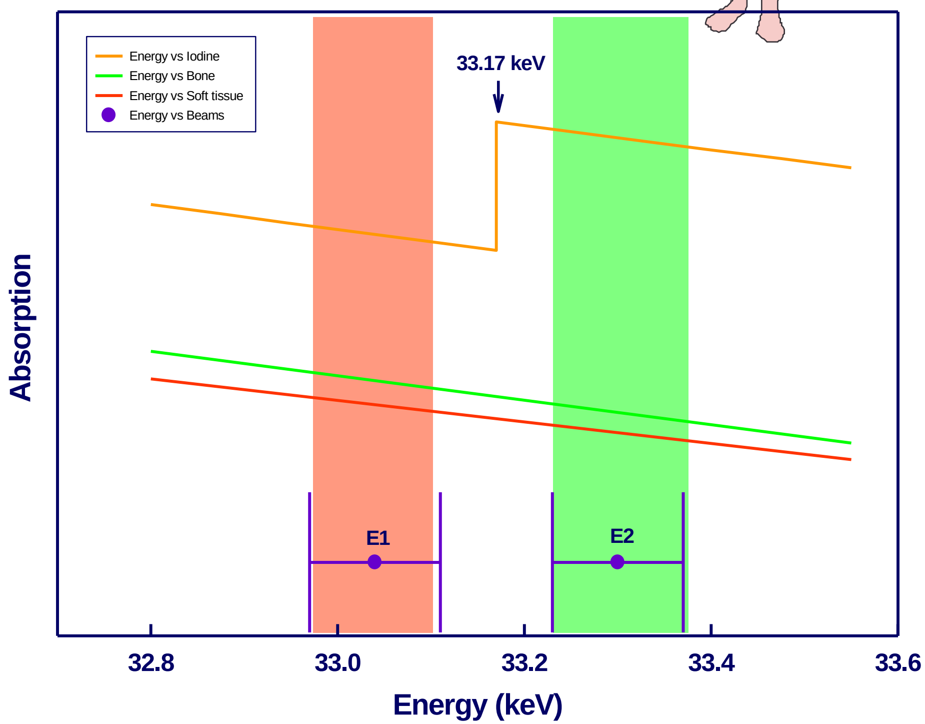


Exploit What Synchrotrons Are Good At

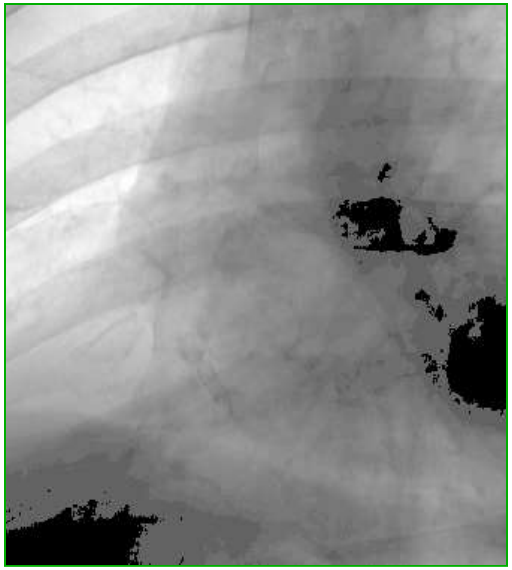
- So there is still work to do optimising imaging with ionising radiation
  - Eliminating artefacts
  - Reducing Dose
- Synchrotron is a great tool for performing medical physics studies
  - Synchrotron beams can be monochromated
    - No beam hardening
  - Synchrotron beams are almost parallel
    - No cone beam artefacts
    - Scatter removal with no dose penalty
  - Synchrotron beams can be tuned
    - Select optimal energy
- We can do studies of better x-ray imaging and develop new methodologies

Subtraction Radiography

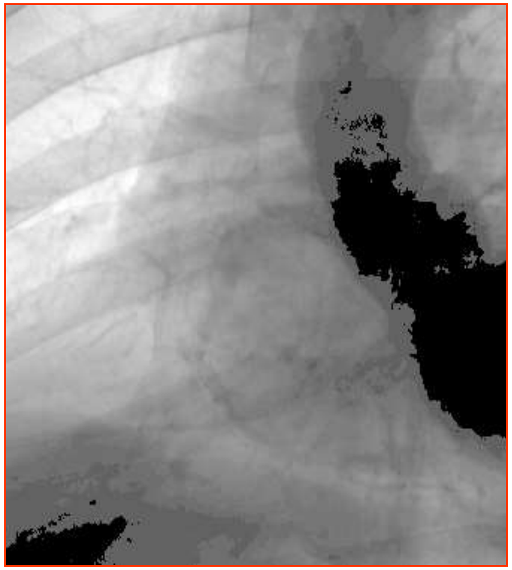




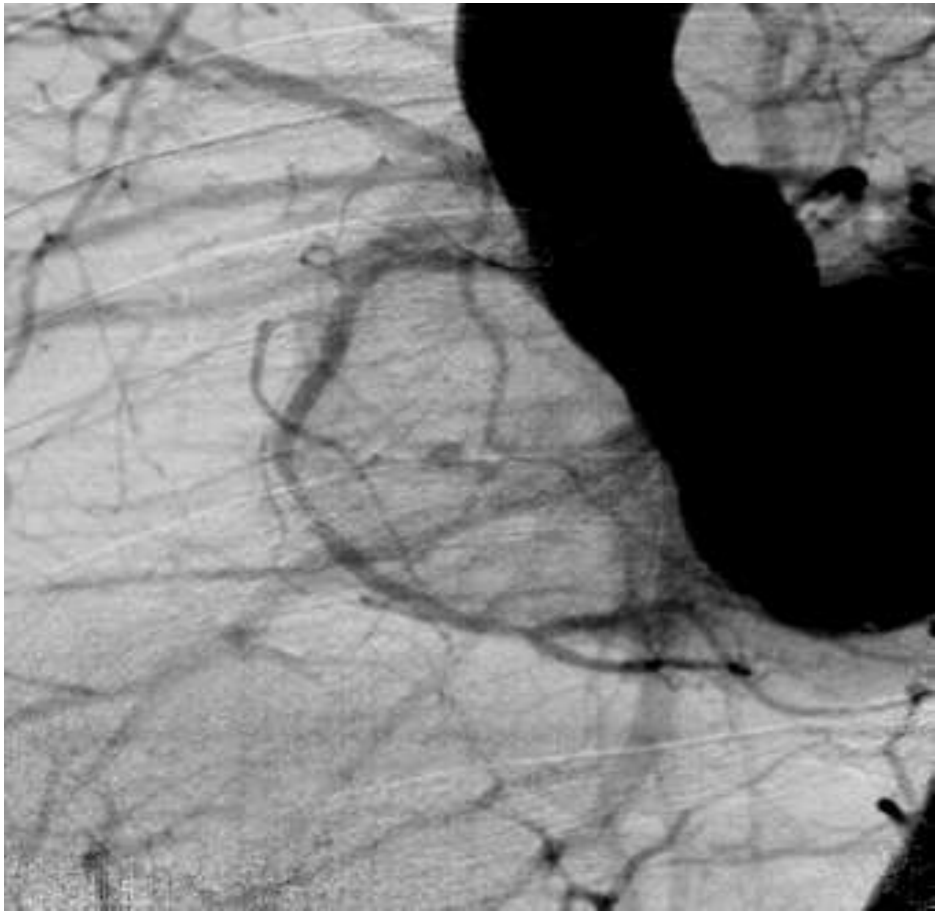
High



Low



Patient 1 - weight: 70 kg - iodine: 42ml



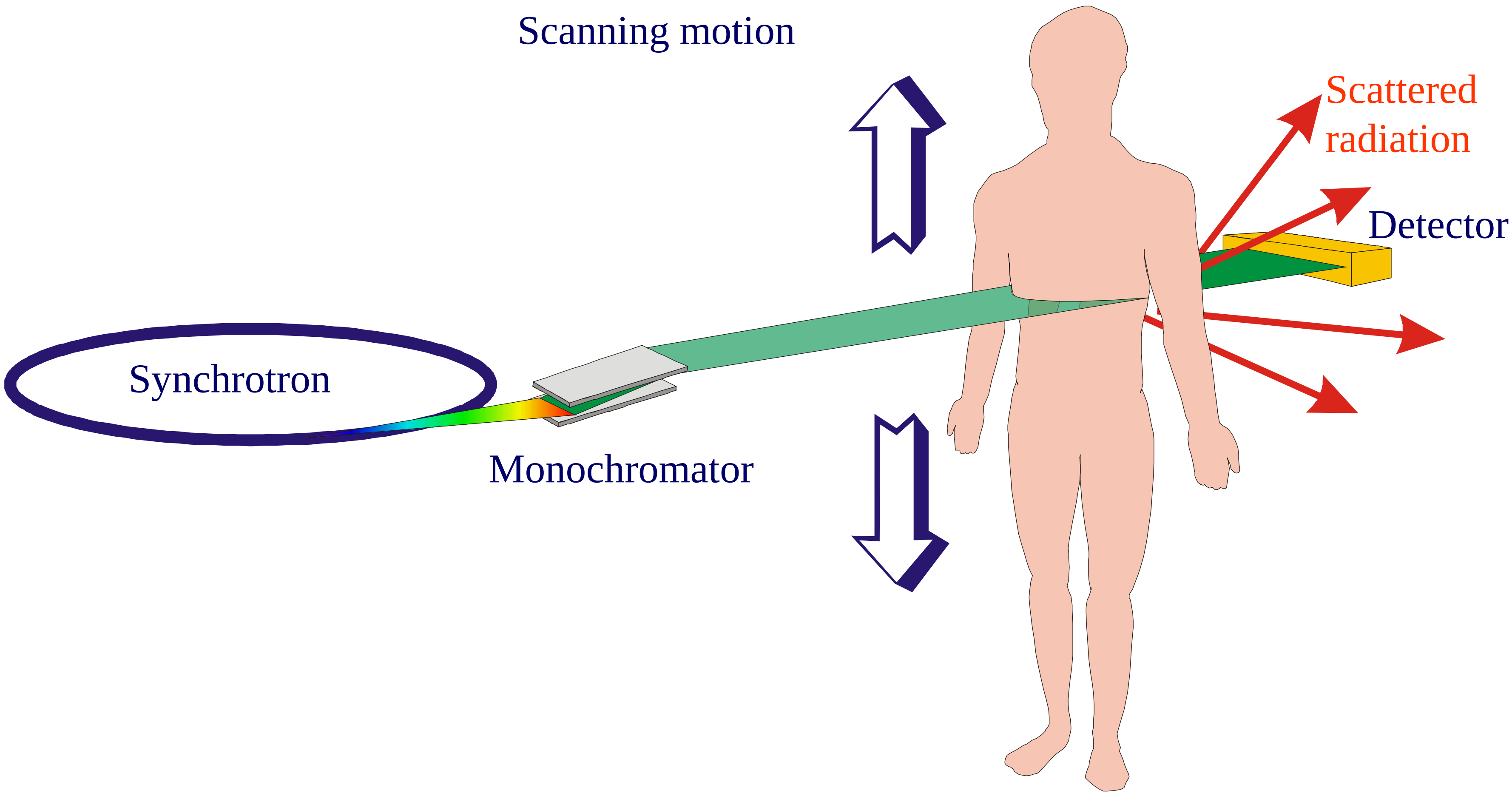
Synchrotron IV injection
n.b. 2 – LAO 40

Conventional angiography
Intra arterial injection

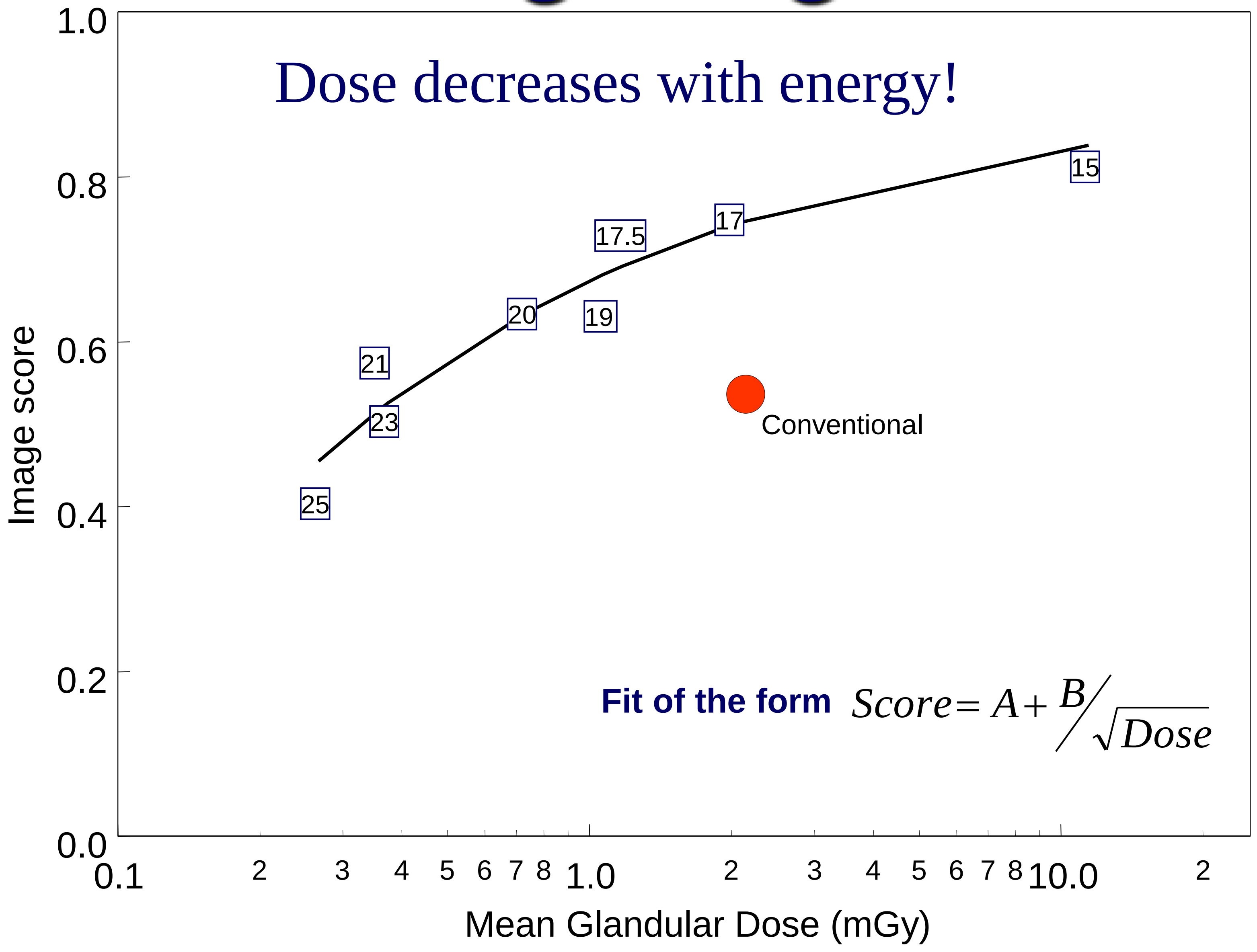
Synchrotron Clinical Studies

- Coronary Angiography
  - Several hundred patients in Hamburg and at ESRF
  - Synchrotron sensitivity allowed venous injection rather than arterial as is required in hospital
  - Not all coronary arteries always visualised well

Synchrotron Radiography



Slot Scanning Image Scores



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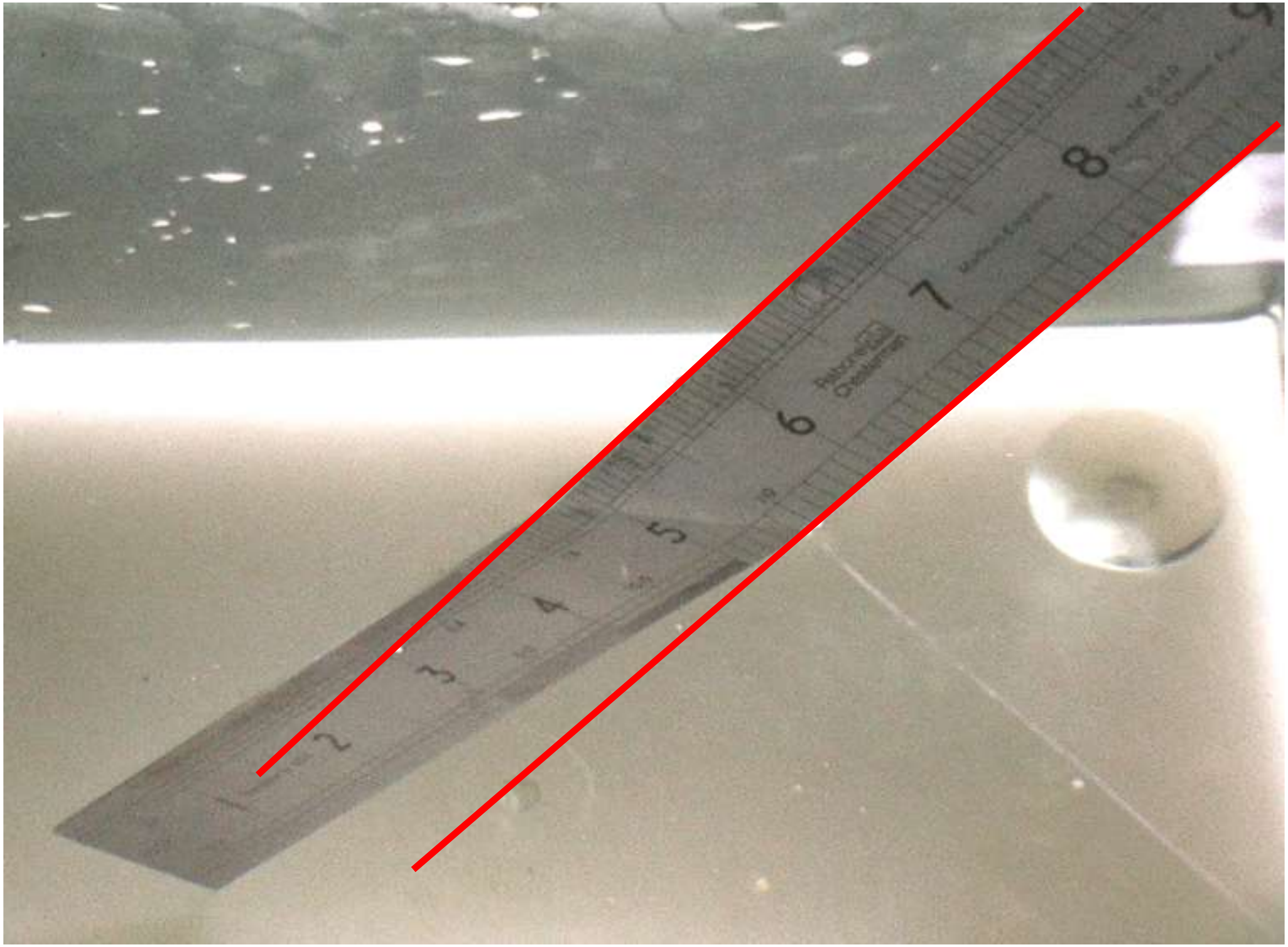
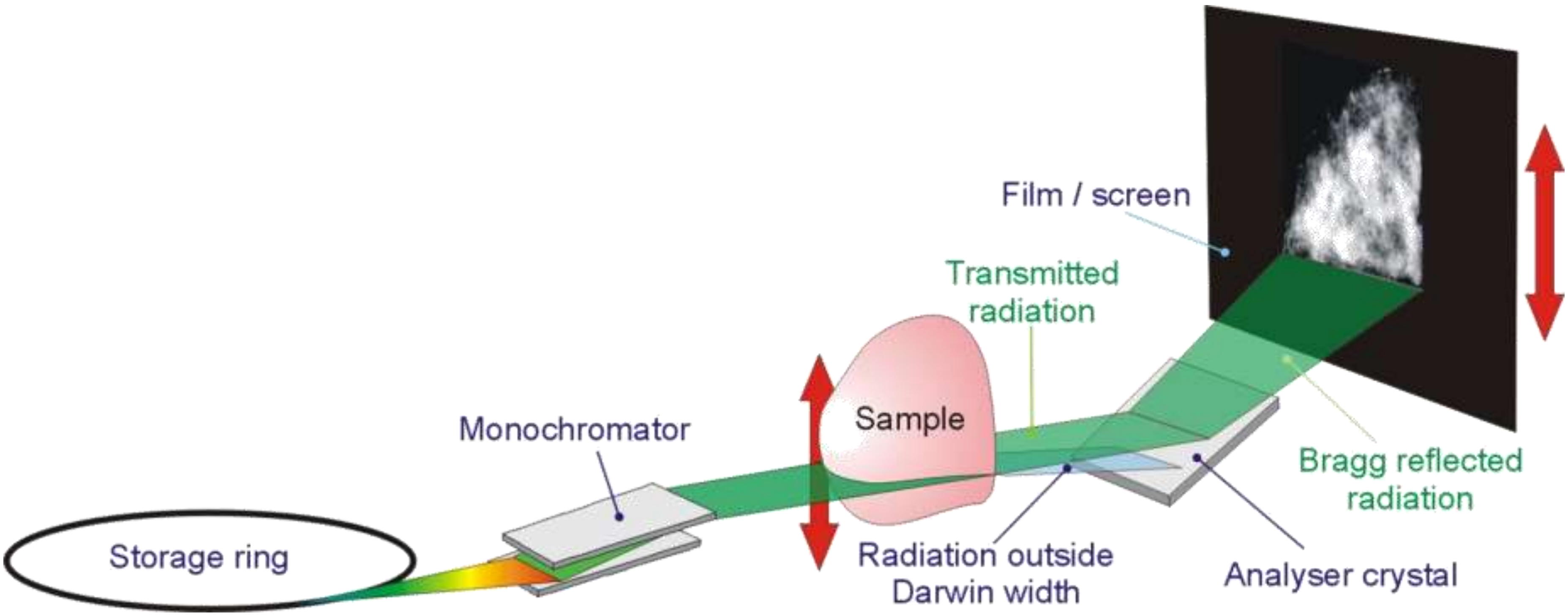
Refraction

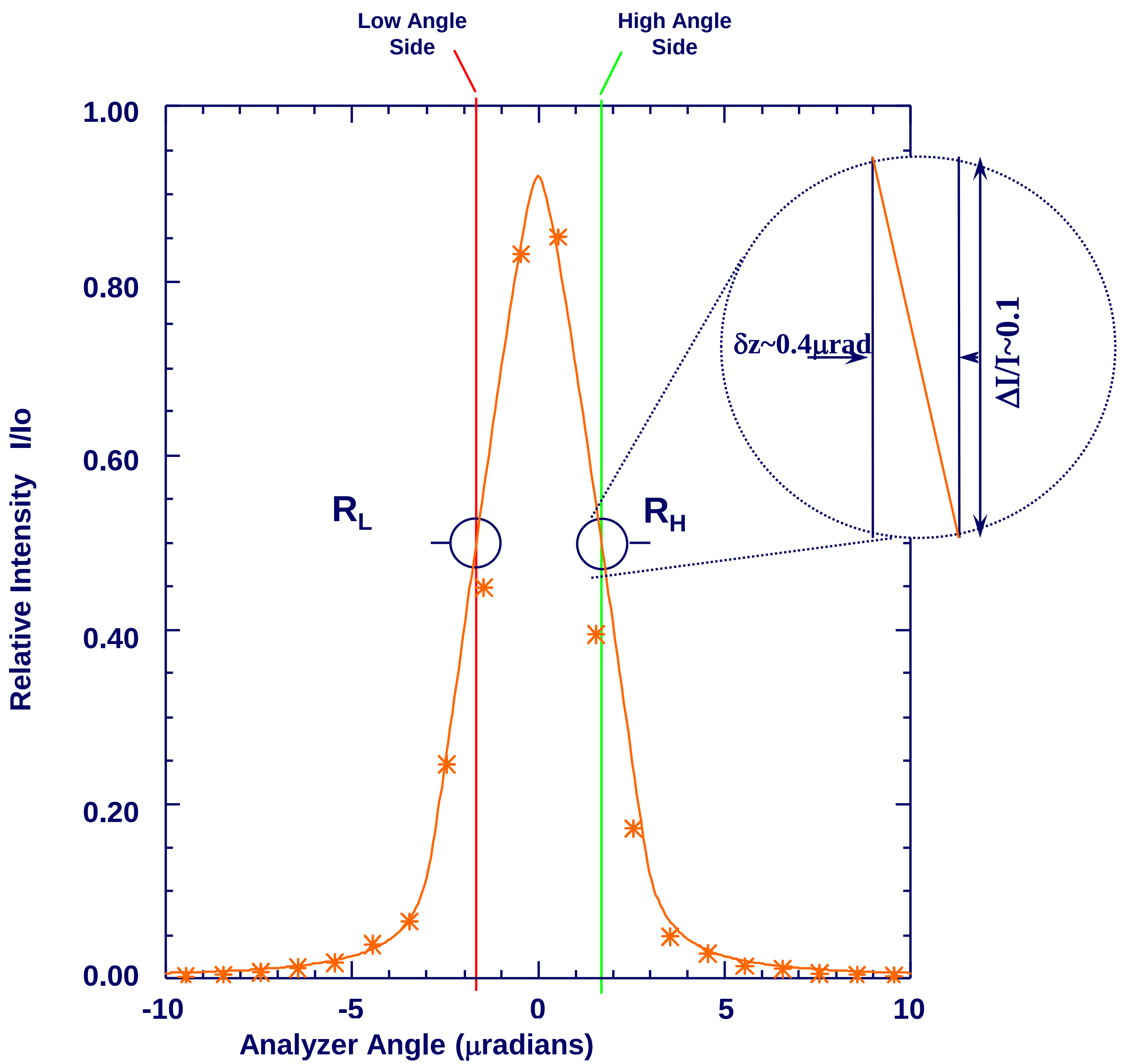


Analyser Based Imaging

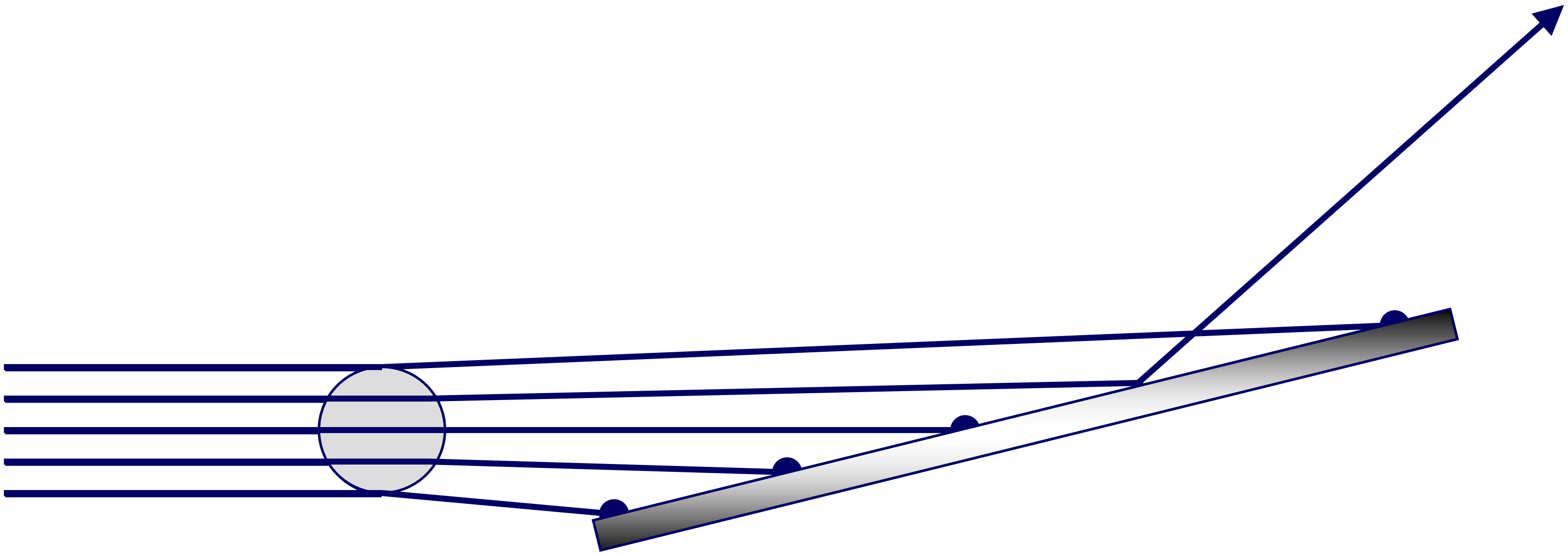
Sometimes called Diffraction Enhanced Imaging



Crystal Rocking Curve

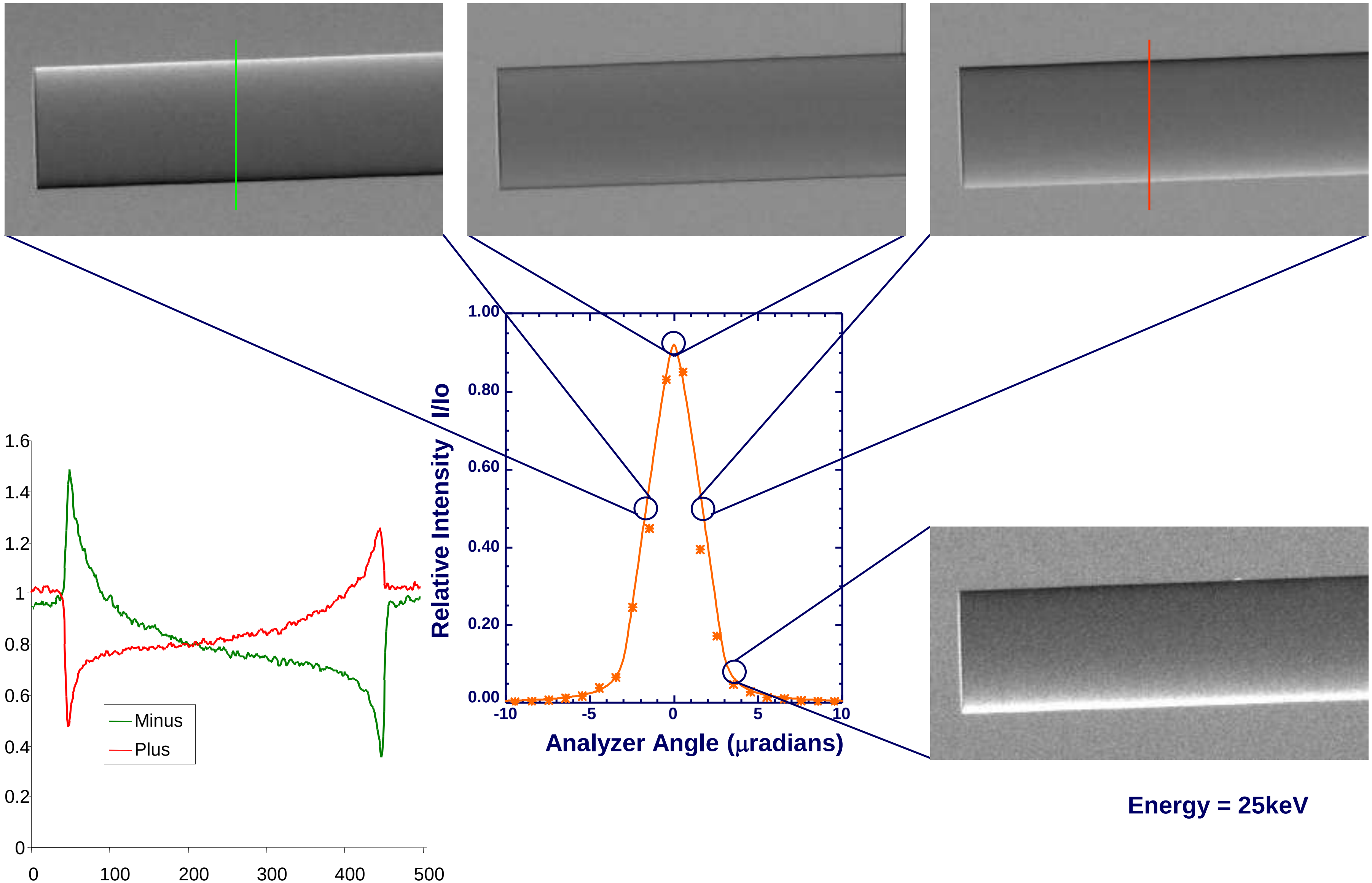


Rocking Curve



Refractive index for X-rays is less than 1 by about 1 part in a million

ABI How it works



ABI Mathematics

- I_L & I_H = Intensities on low and high angle sides of rocking curve
- $Grad_L$ & $Grad_H$ = Gradients of low and high angle sides of rocking curve
- I_R is intensity
- $\Delta\theta_z$= refraction angle

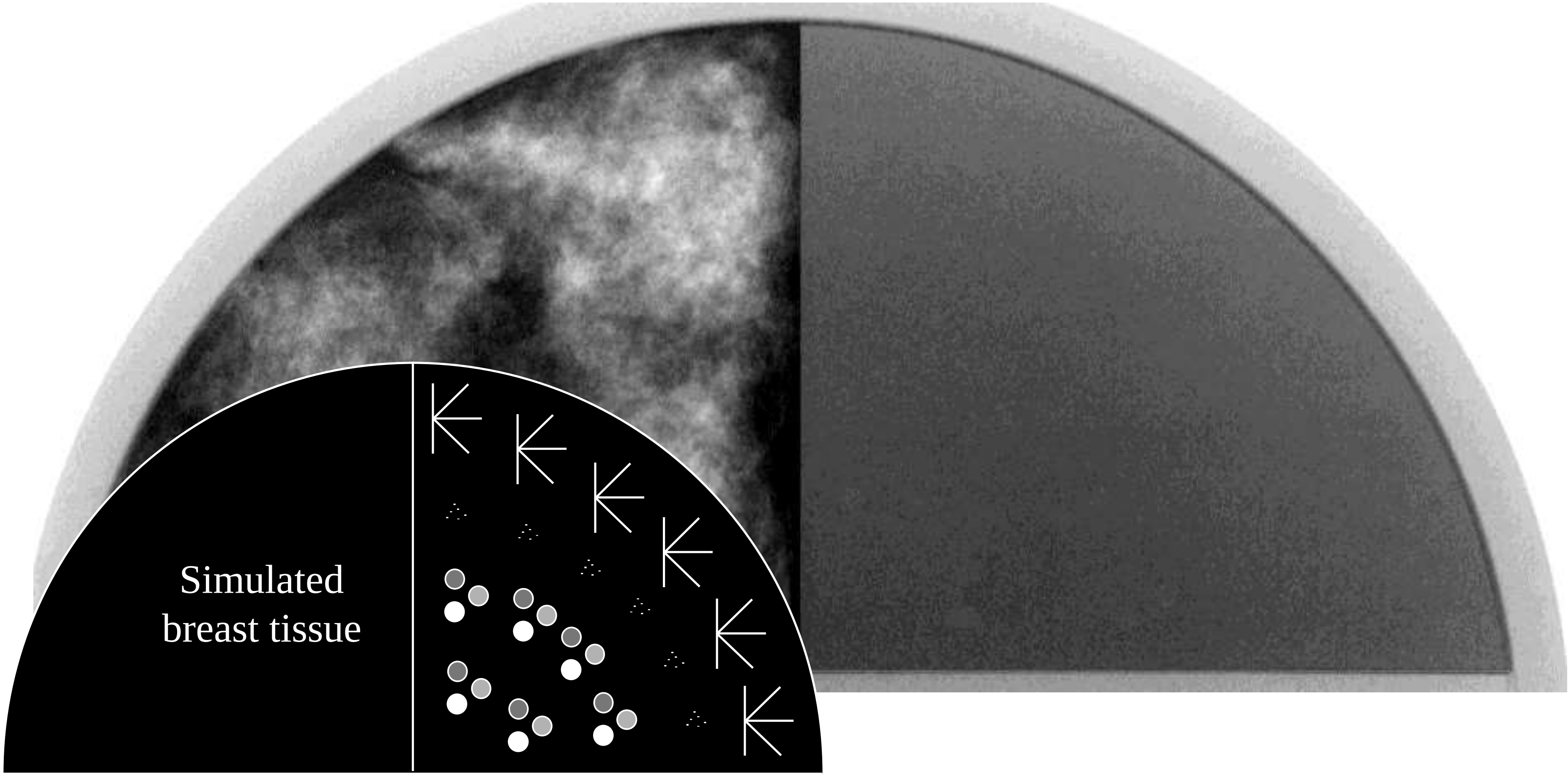
Given

$$I_L = I_R \cdot \left(R_L + Grad_L \cdot \Delta\theta_Z\right)$$

$$I_H = I_R \cdot \left(R_H + Grad_H \cdot \Delta\theta_Z\right)$$

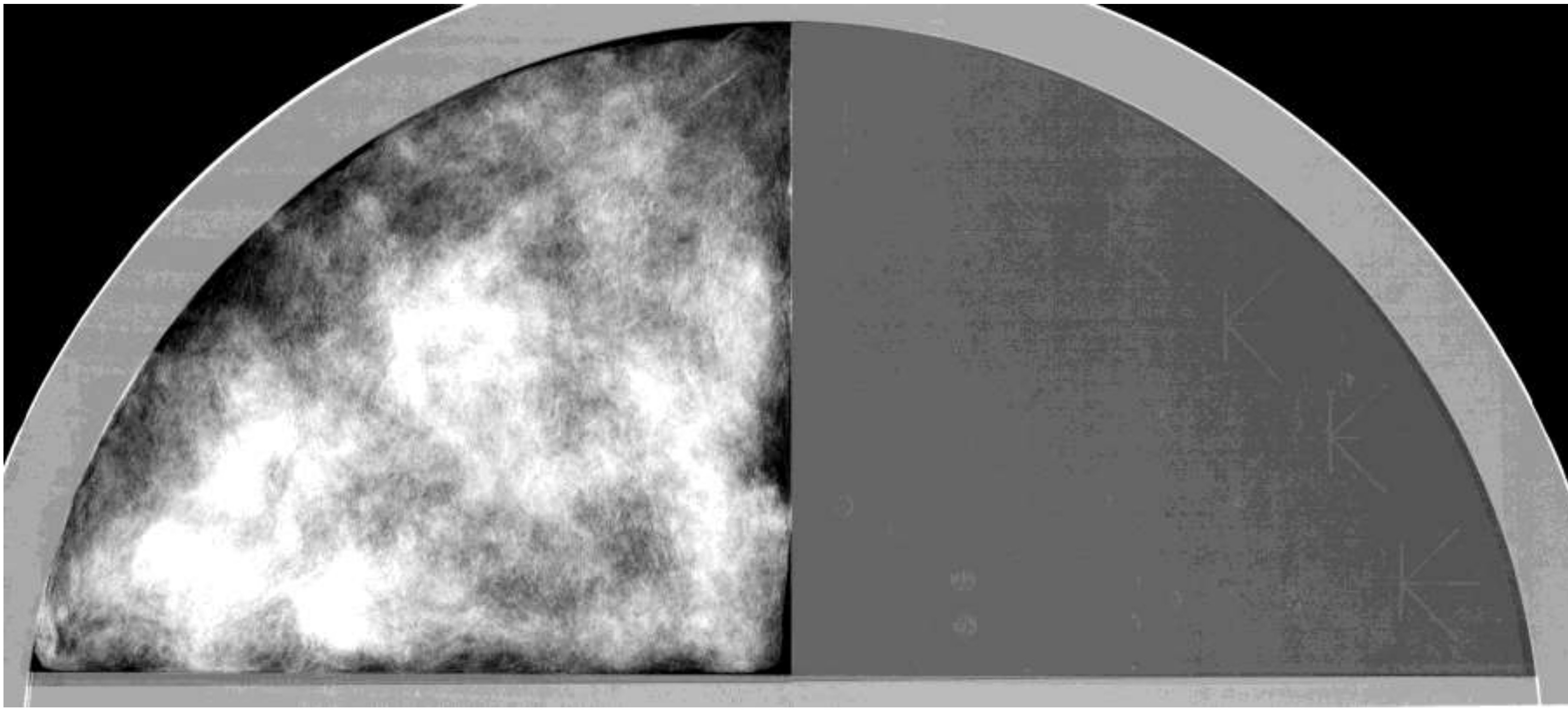
$$\mathrm{Find}\left(I_R, \Delta\theta_Z\right) \rightarrow \begin{pmatrix} \dfrac{Grad_H \cdot I_L - Grad_L \cdot I_H}{Grad_H \cdot R_L - Grad_L \cdot R_H} \\ \dfrac{I_H \cdot R_L - I_L \cdot R_H}{Grad_H \cdot I_L - Grad_L \cdot I_H} \end{pmatrix}$$

TORMam Conventional



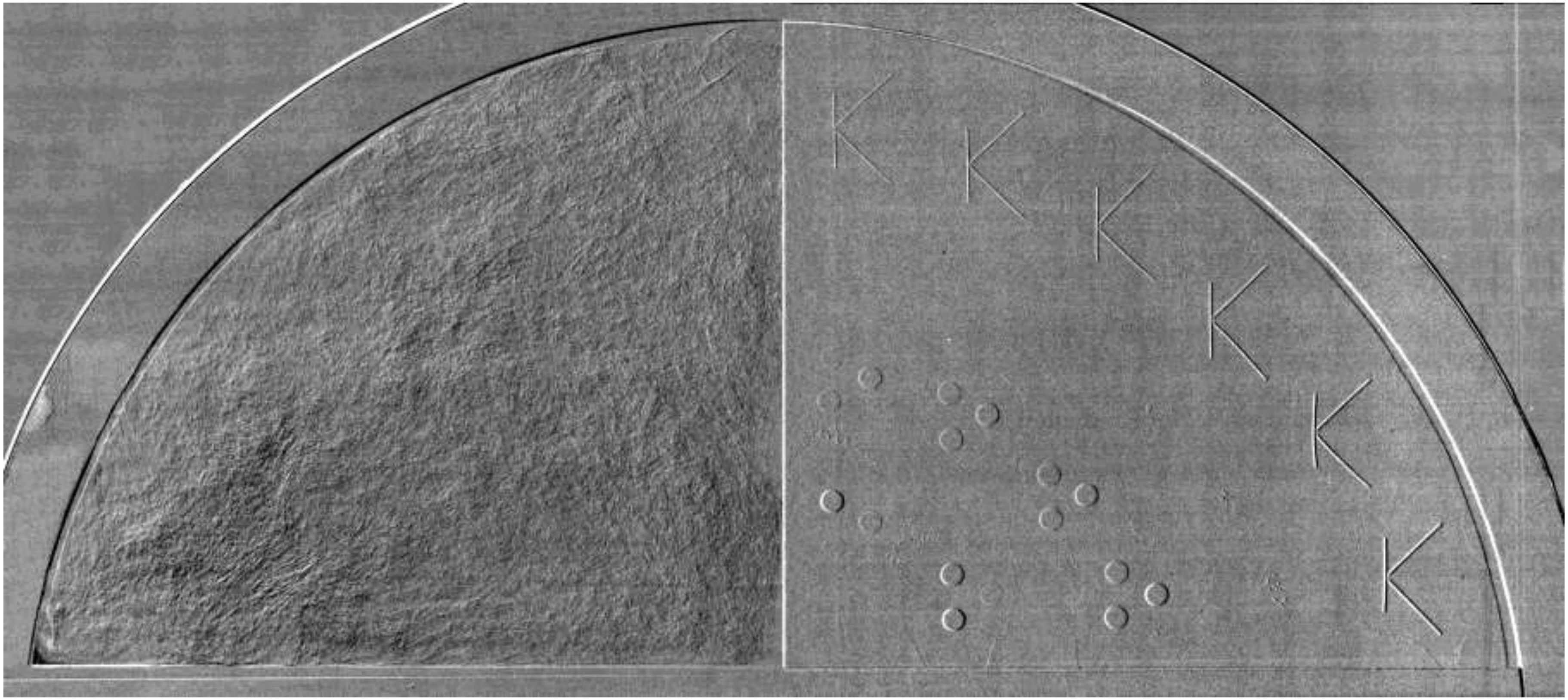
Spectrum = Mo:Mo 28kVp

TORMAM Peak



Energy = 20keV

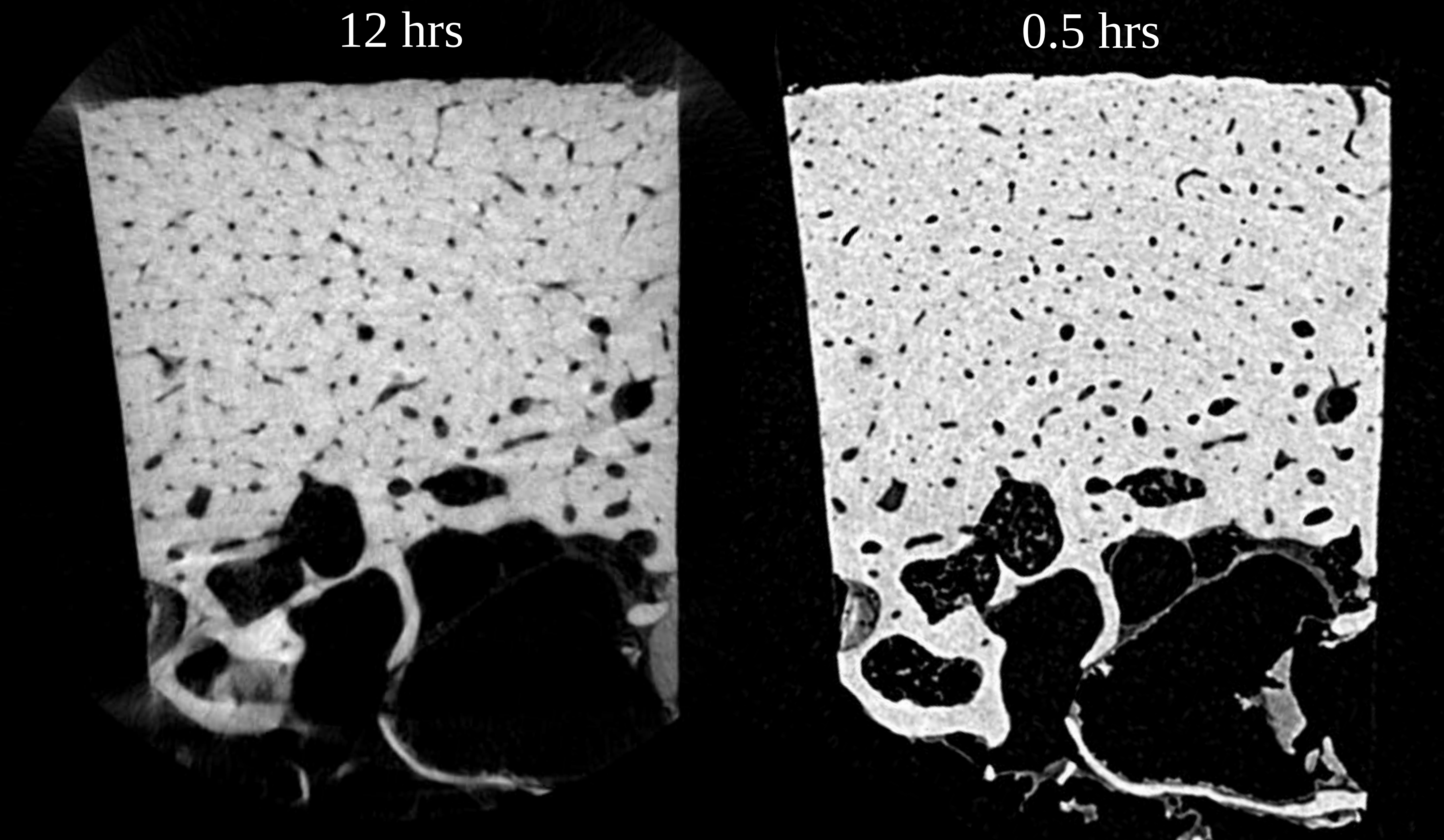
TORMAM Refraction



Energy = 20keV

Advantages of synchrotron micro-CT

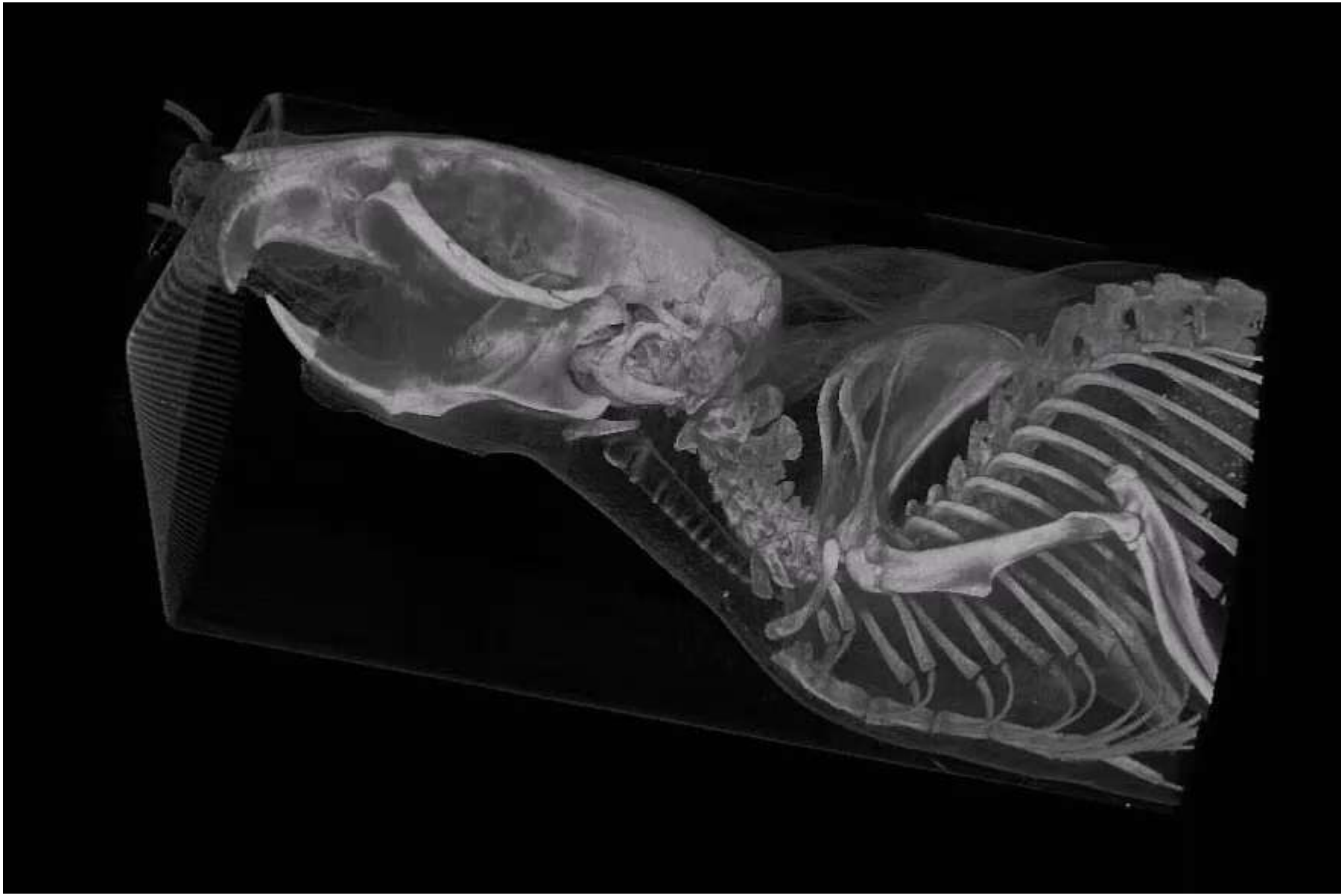
12 hrs | 0.5 hrs



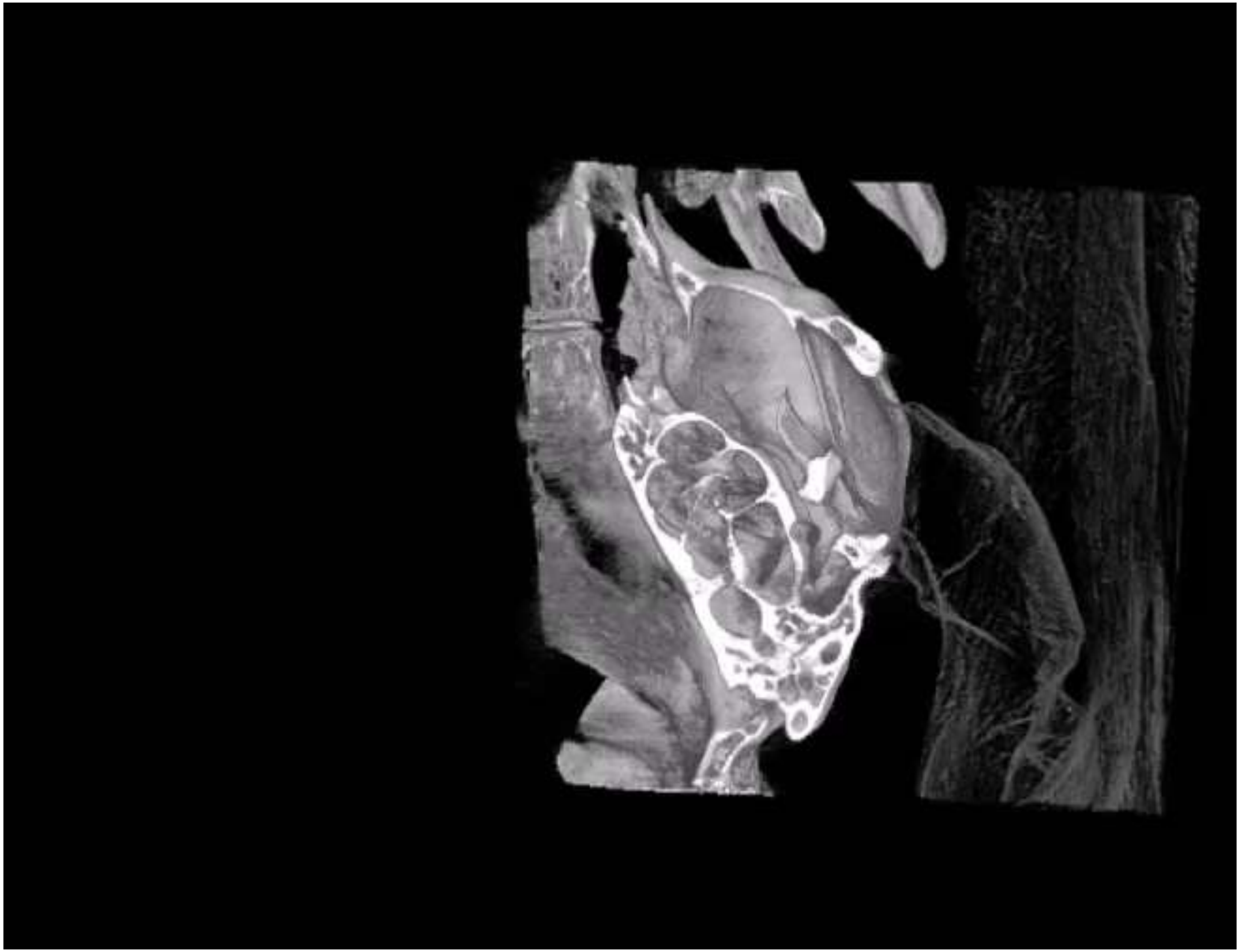
SkyScan 1072 (Desktop) 7 μm | Spring8 (Synchrotron) 12 μm

David Cooper, UofS; David Thomas, Melbourne

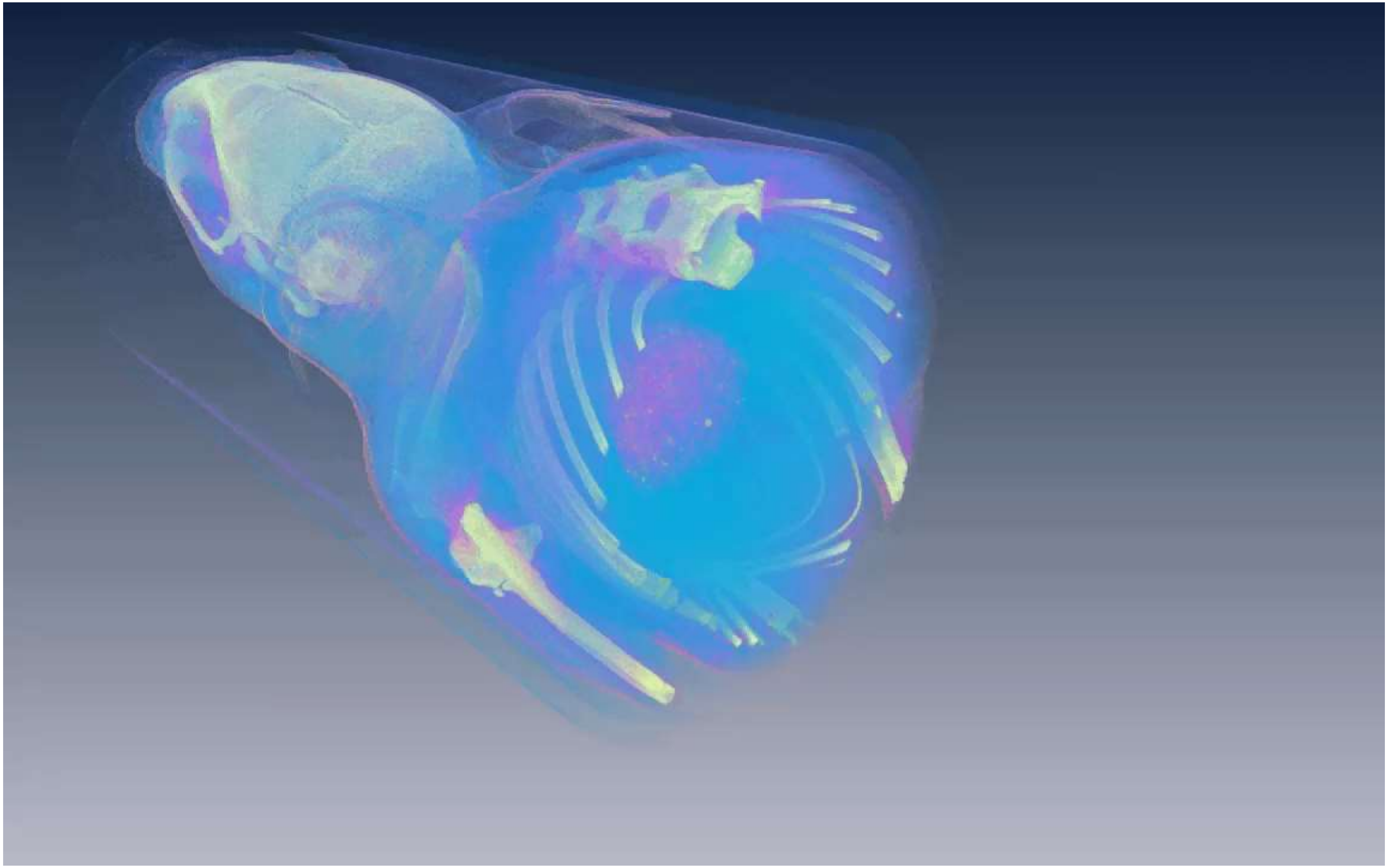
Mouse CT



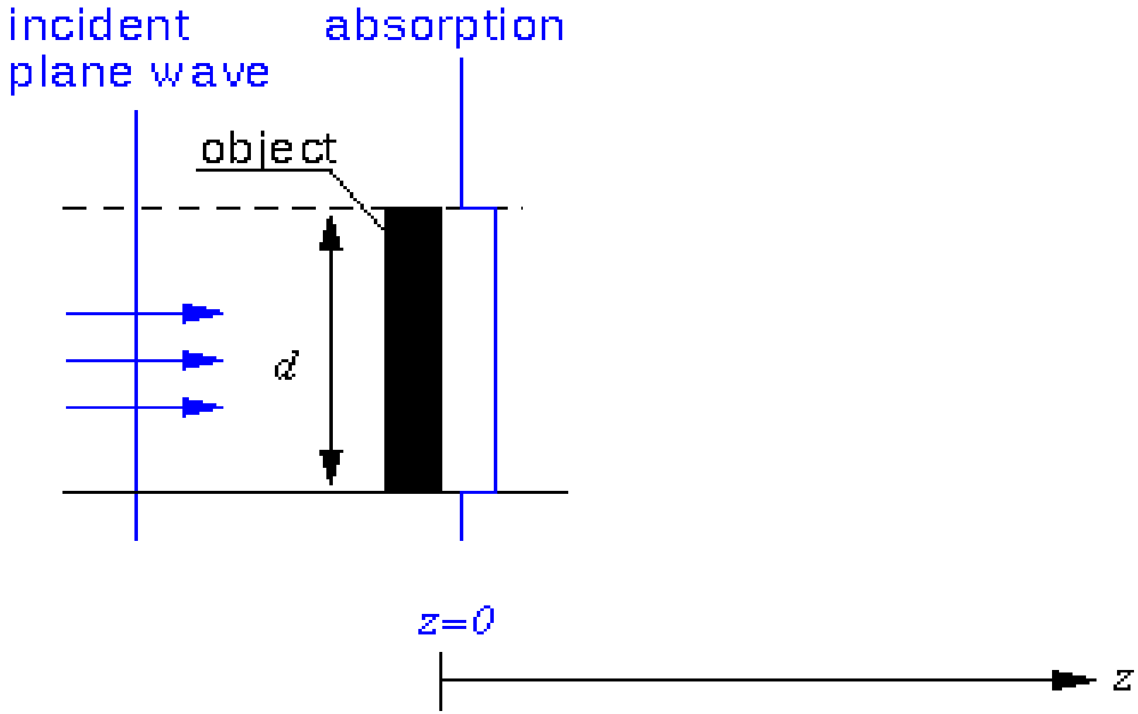
Mouse Cochlea



Mouse Fly Through



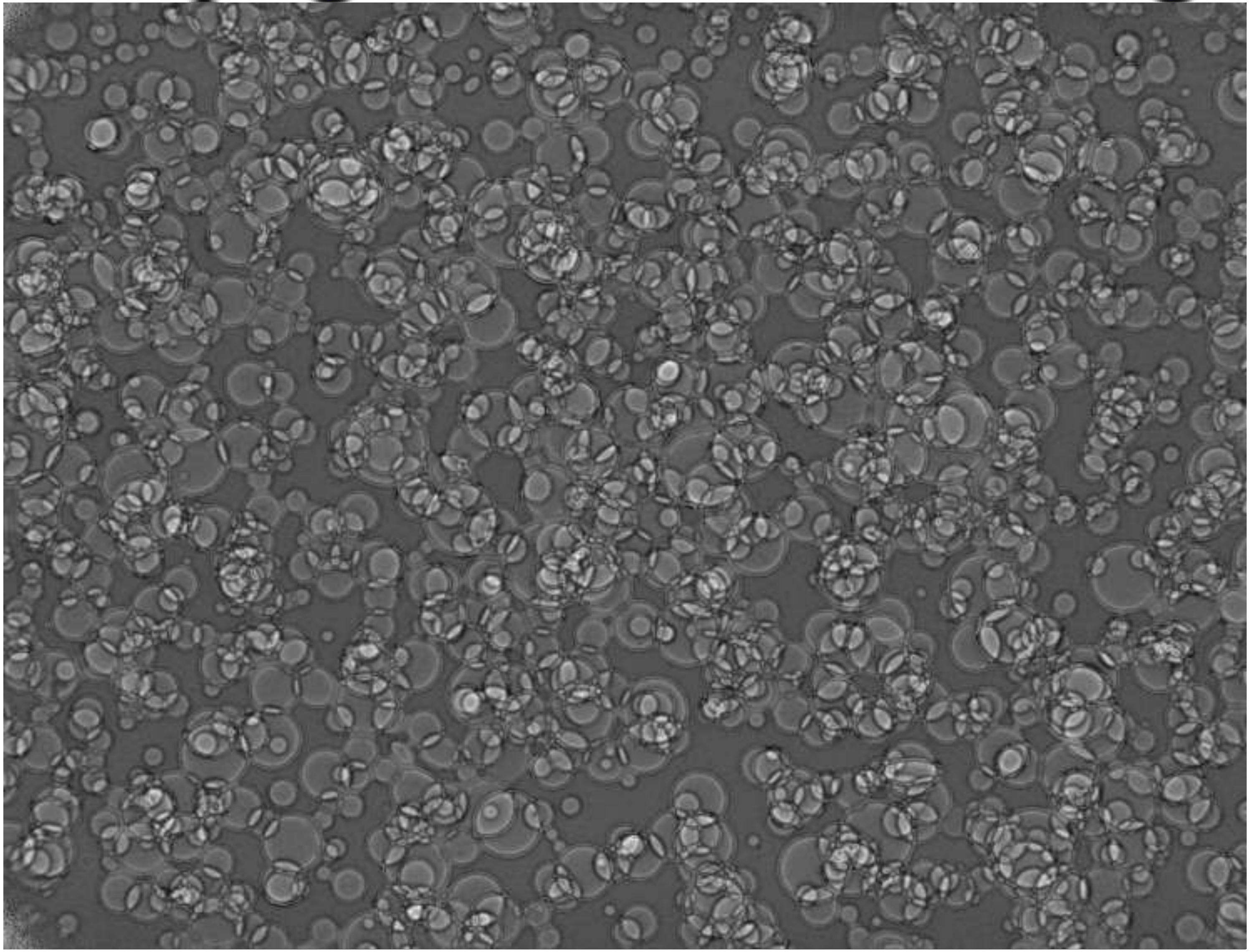
Phase Contrast



$$N_F = \frac{d^2}{\lambda z}$$

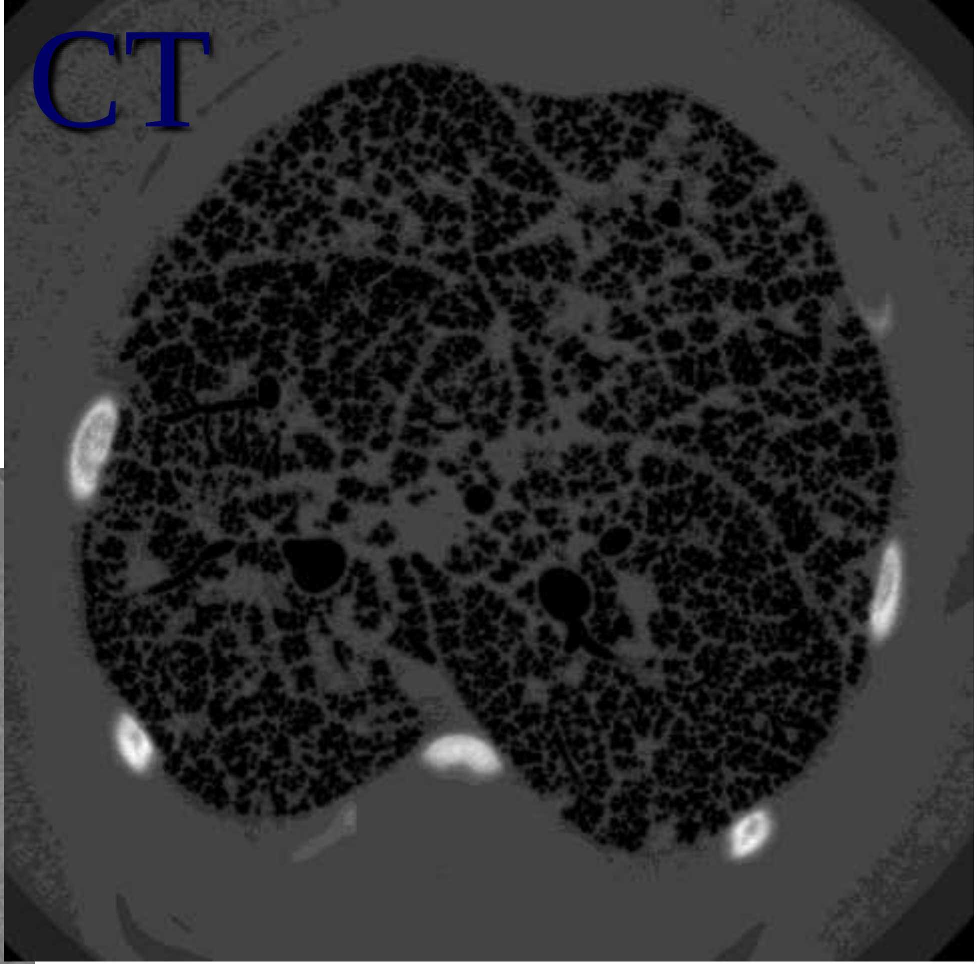
- **Contact:** $N_F >> 1$ **Geometric approximation**
  - The intensity distribution is a pure absorption image.
- **Near field:** $N_F >> 1$ **Geometric approximation**
  - Contrast is given by sharp changes in the refractive index, i. e. at interfaces.
- **Intermediate field:** $N_F \sim 1$ **Fresnel approximation**
  - The image loses more and more resemblance with the object.
- **Far field:** $N_F << 1$ **Far: Fraunhöfer approximation**
  - The image is the Fourier transform of the object transmission function

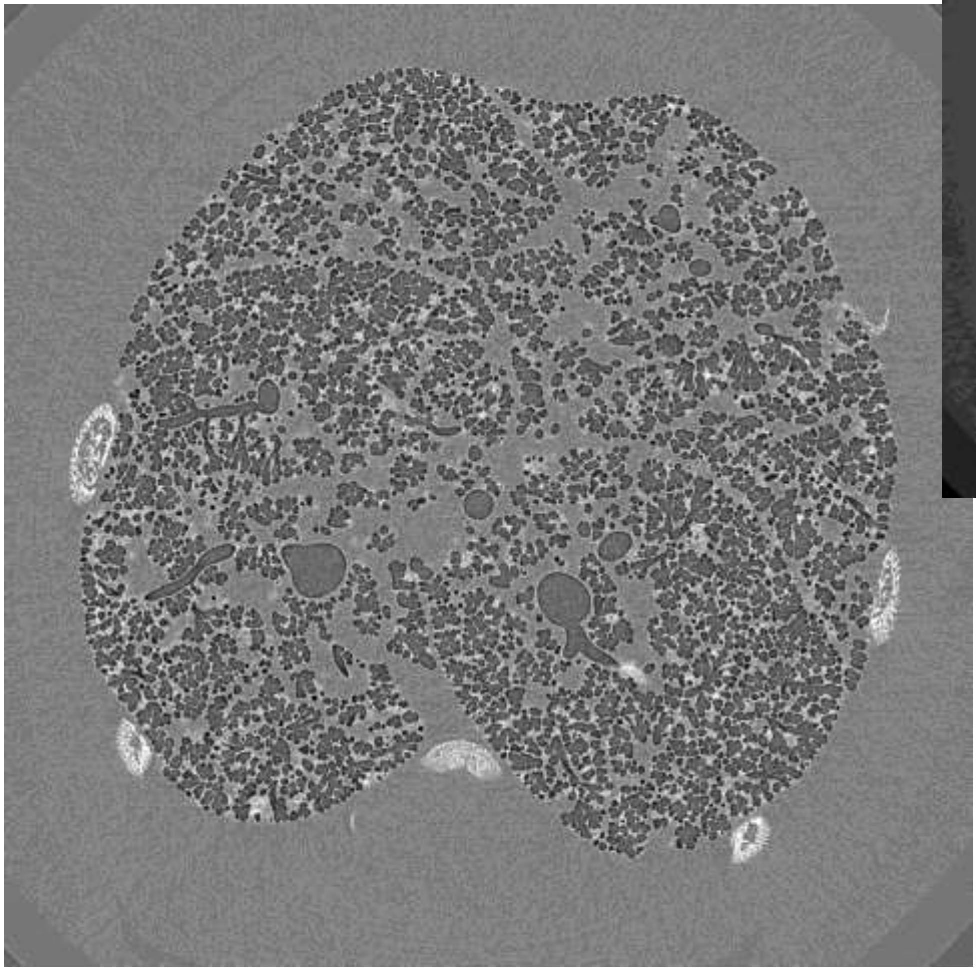
Propagation Based Imaging



147cm

Phase Contrast CT

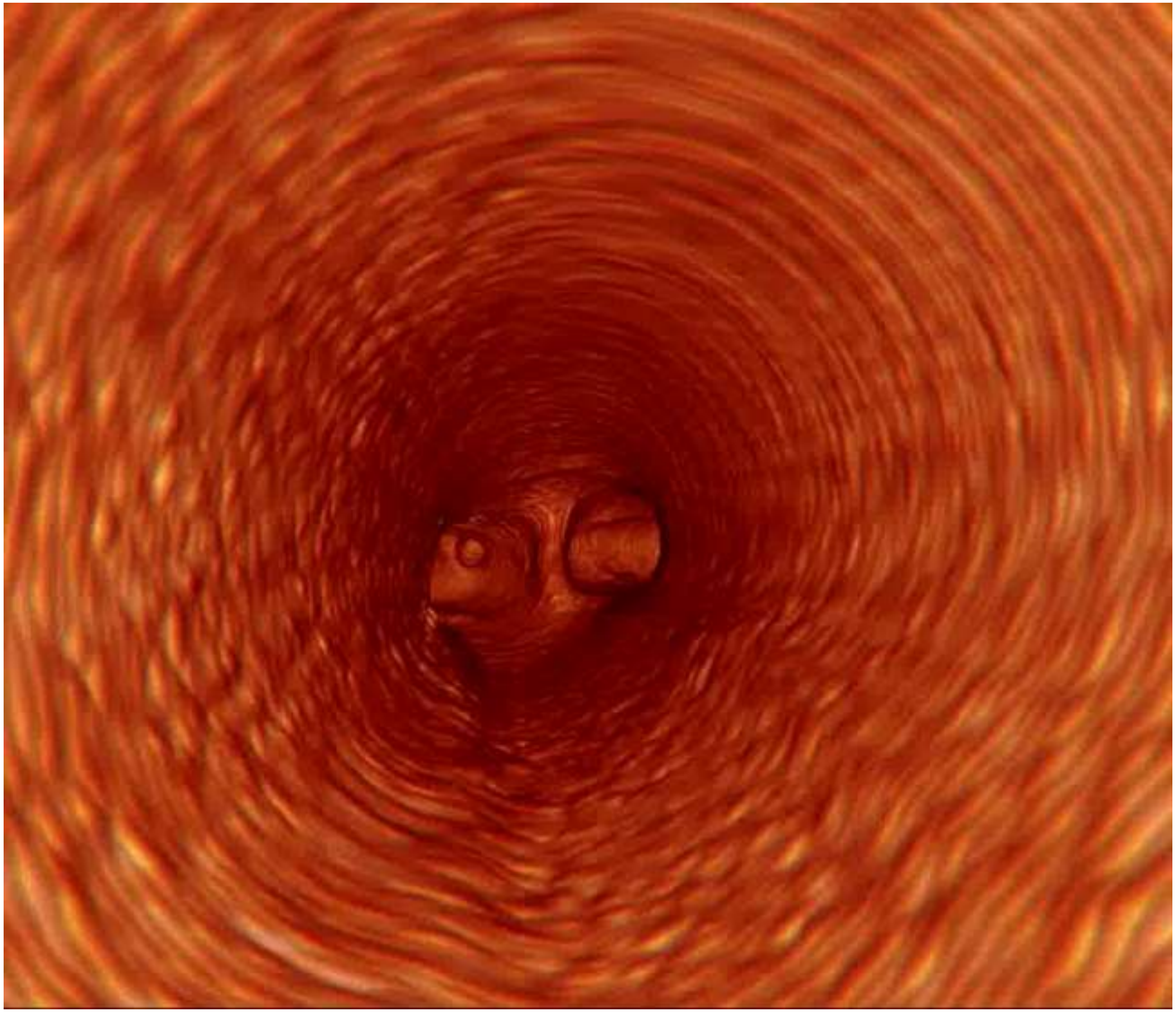




Lungs of newborn rabbit
Propagation distance = 1m
Energy = 24 keV

Beltran, M.A. *et al.*, *Phys Med Biol*, ***56****, 7353-7369, 2011*.

Phase Contrast CT

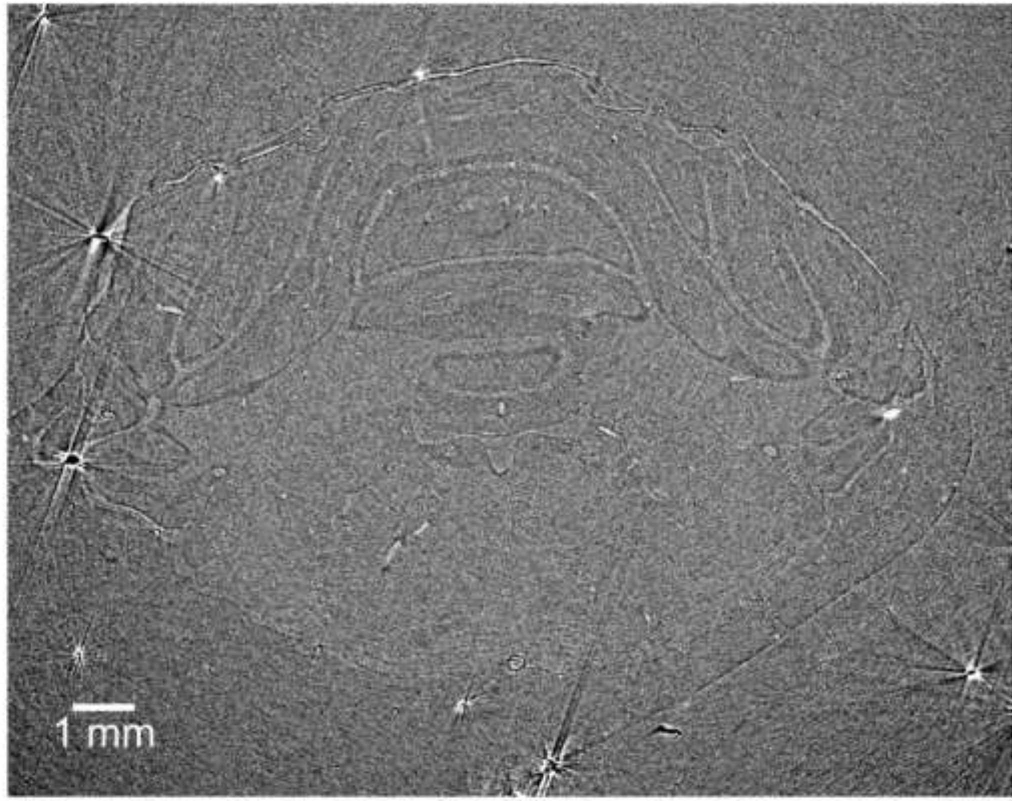


- SNR increased 10x, enabling high quality visualization

Beltran, M.A. *et al*., *Phys Med Biol*, ***56***, *7353-7369, 2011*.

Rat Brain in agarose gel

(a)

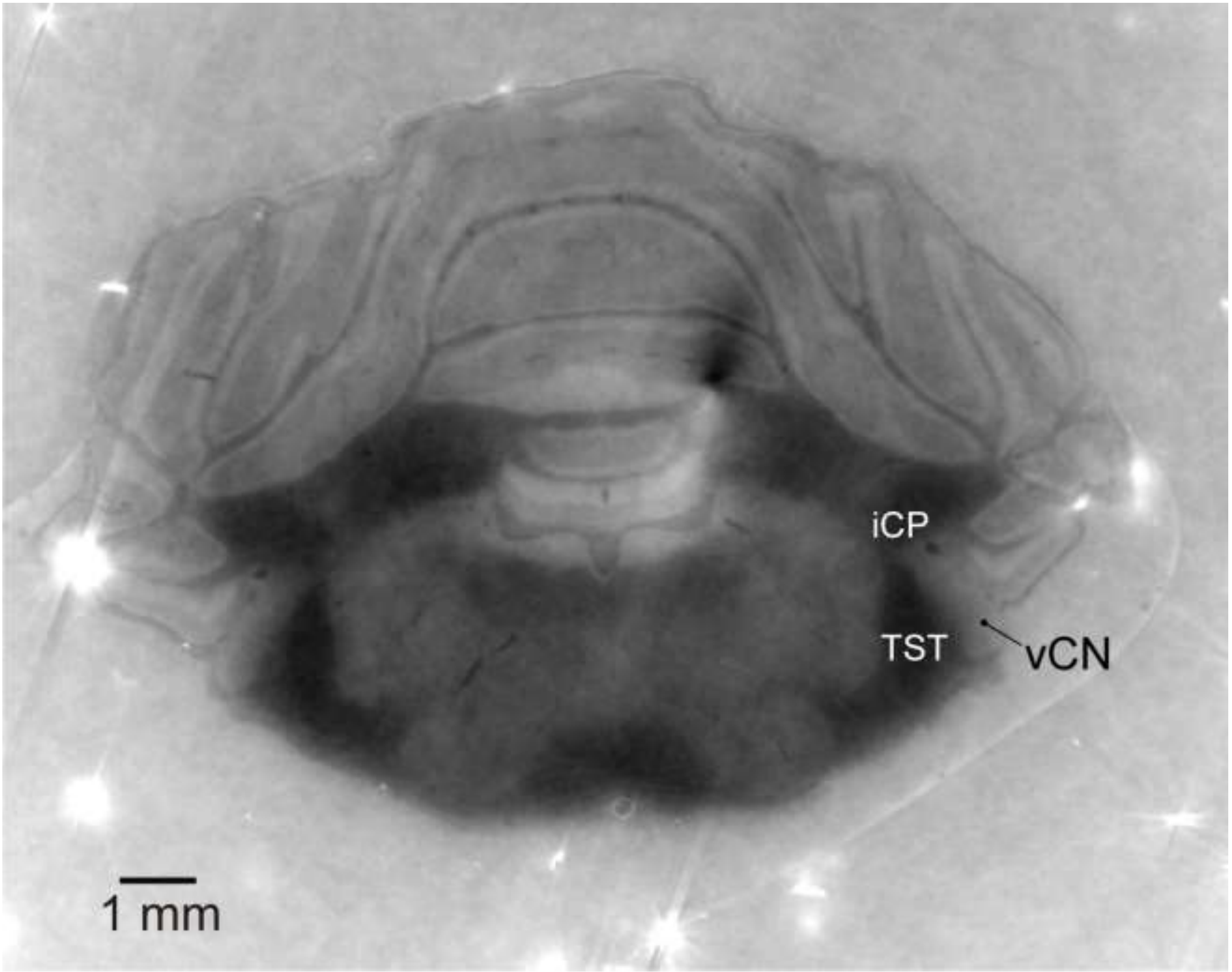


(b)

Brain undetectable in projection image (a), and faintly visible with 5m propagation distance (b) in CT reconstruction. Energy = 24 keV.

Beltran, M.A. *et al*., *Phys Med Biol*, ***56***, *7353-7369, 2011*.

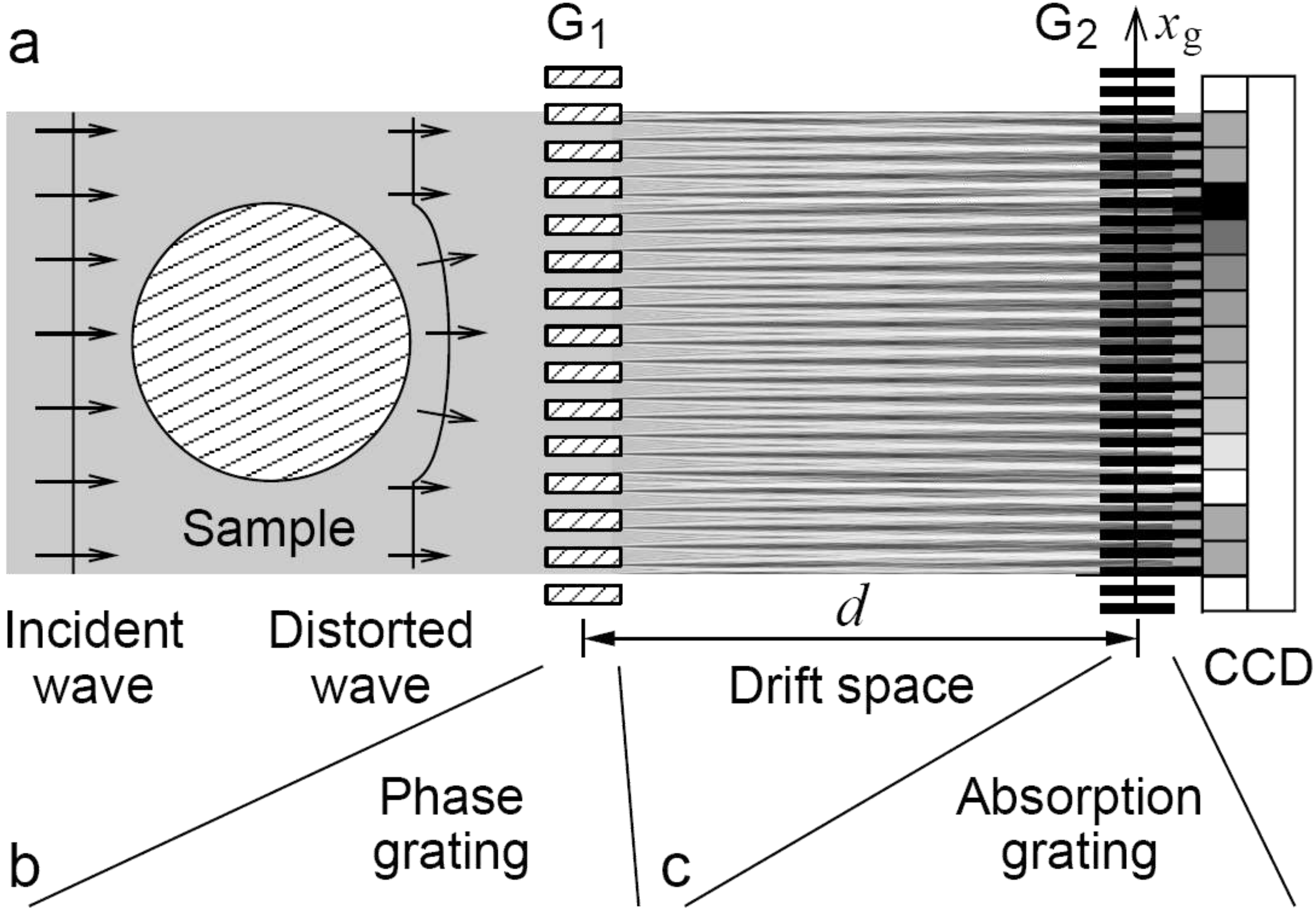
Rat Brain in agarose gel



Phase retrieval renders structures of the brain highly visible against the noise.
Improvement in SNR of 200x!

Beltran, M.A. *et al*., *Phys Med Biol*, ***56***, *7353-7369*, *2011*.

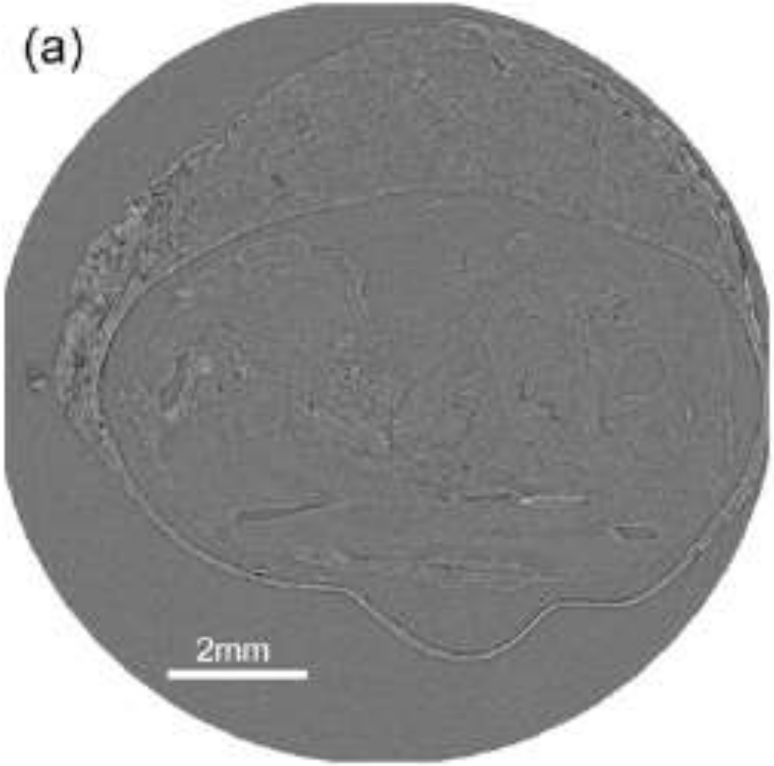
Grating Interferometry



Timm Weitkamp et al Vol. 12, No. 16 / OPTICS EXPRESS 6296

Phase Contrast : Mouse Embryo

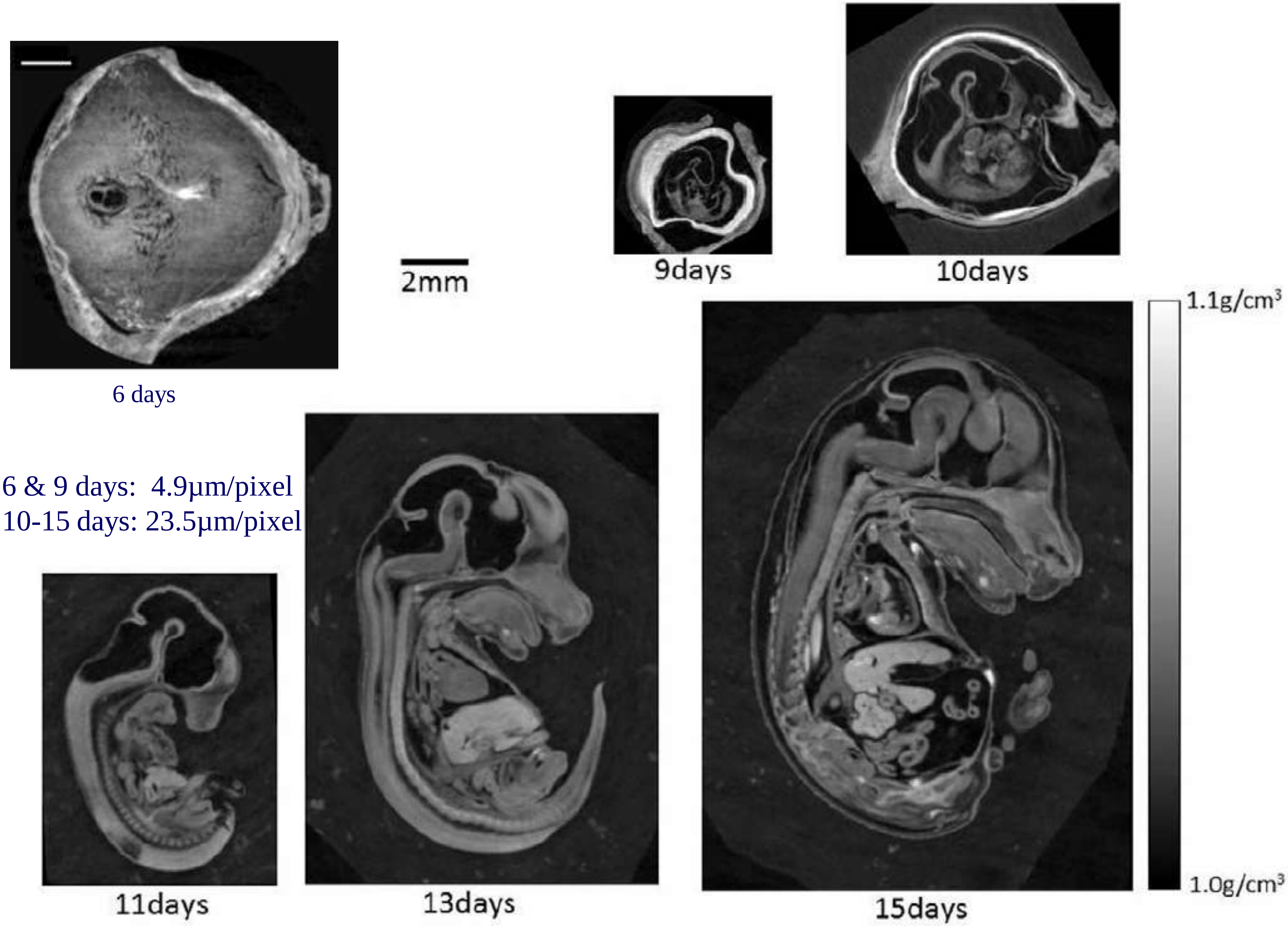
Absorption CT



Phase CT

Hoshino M et al Biology Open 1, 269–274

Phase Contrast : Mouse Embryo



6 days

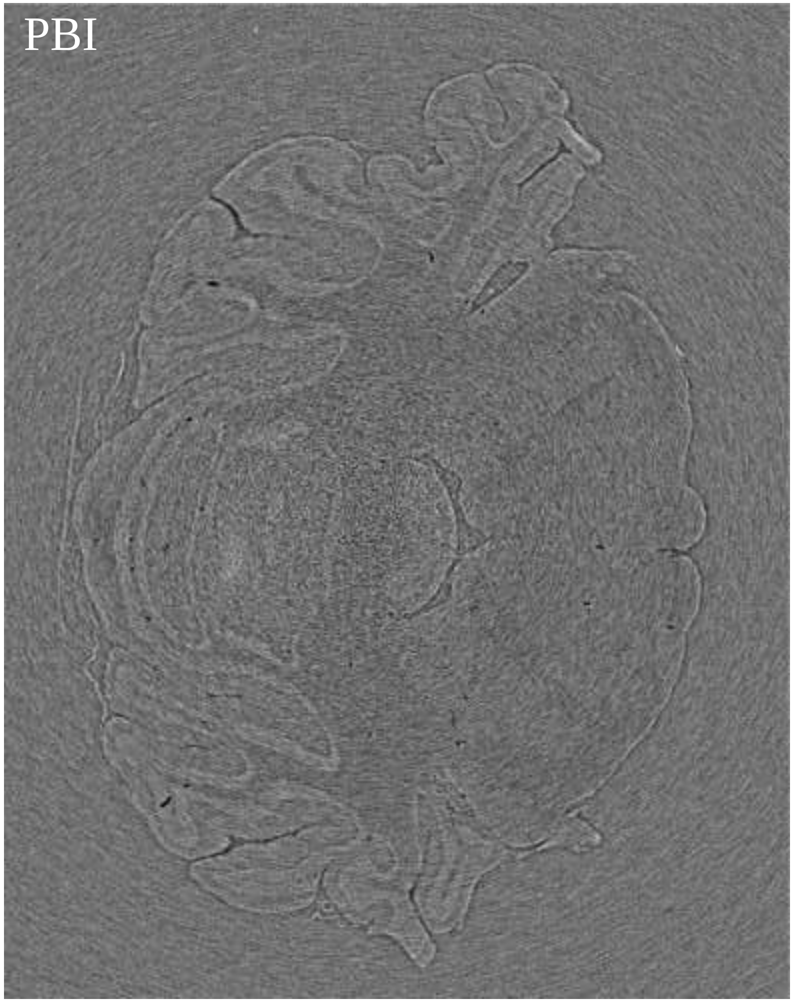
6 & 9 days: 4.9µm/pixel
10-15 days: 23.5µm/pixel

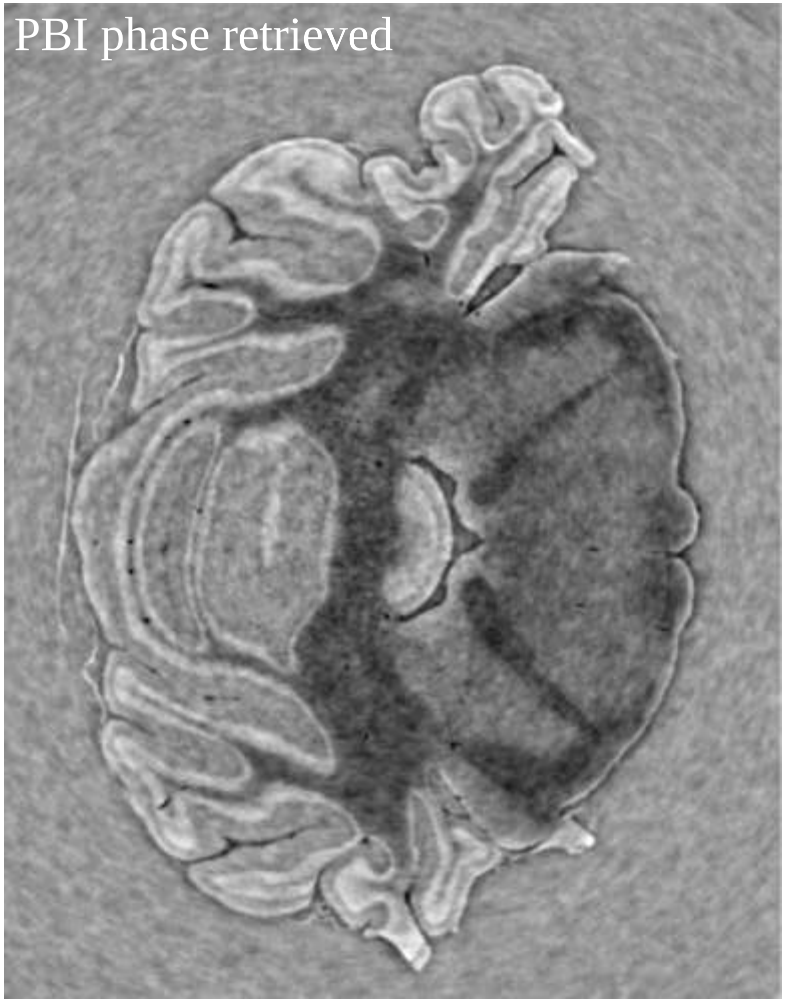
Hoshino M et al Biology Open 1, 269–274

Phase Contrast: Mouse Embryo

Hoshino M et al Biology Open 1, 269–274

Synchrotron Brain Imaging

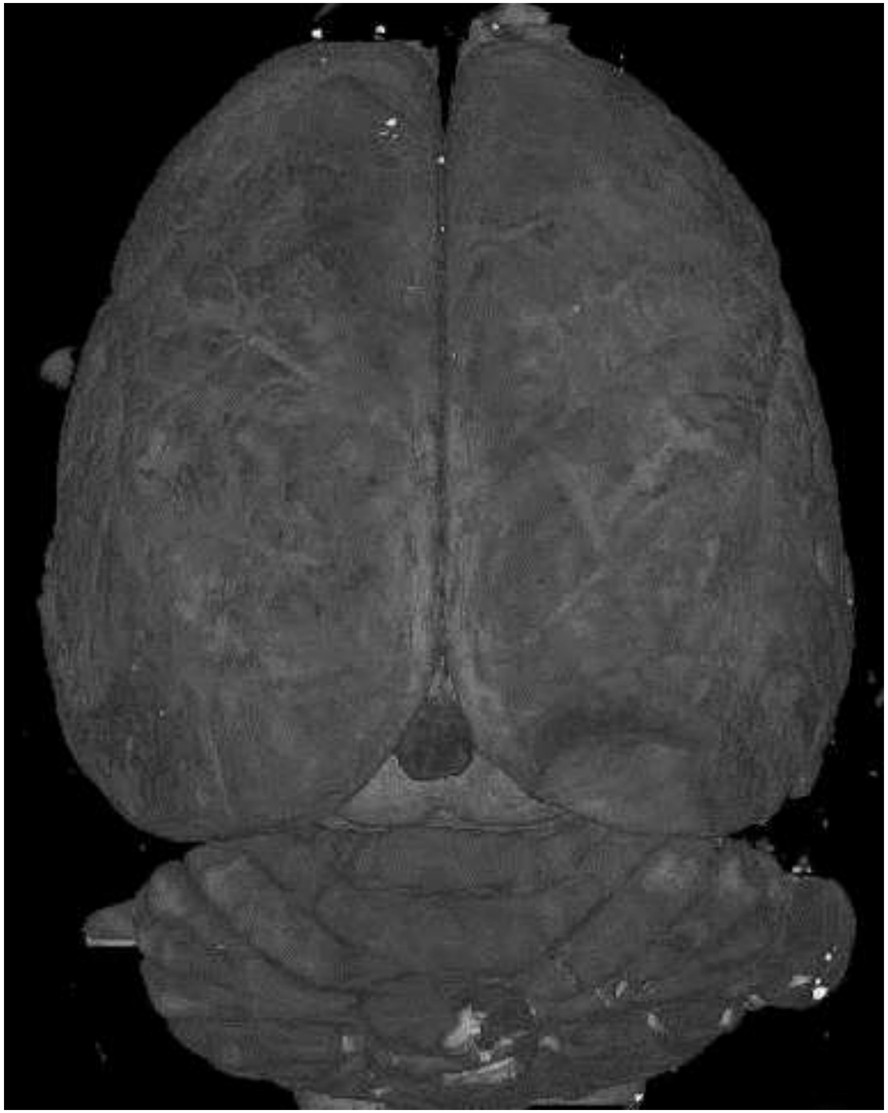




3600 projections
3m propagation distance
1s/image

K Uesugi & M Hoshino JASRI Spring-8

Phase Contrast: Brain

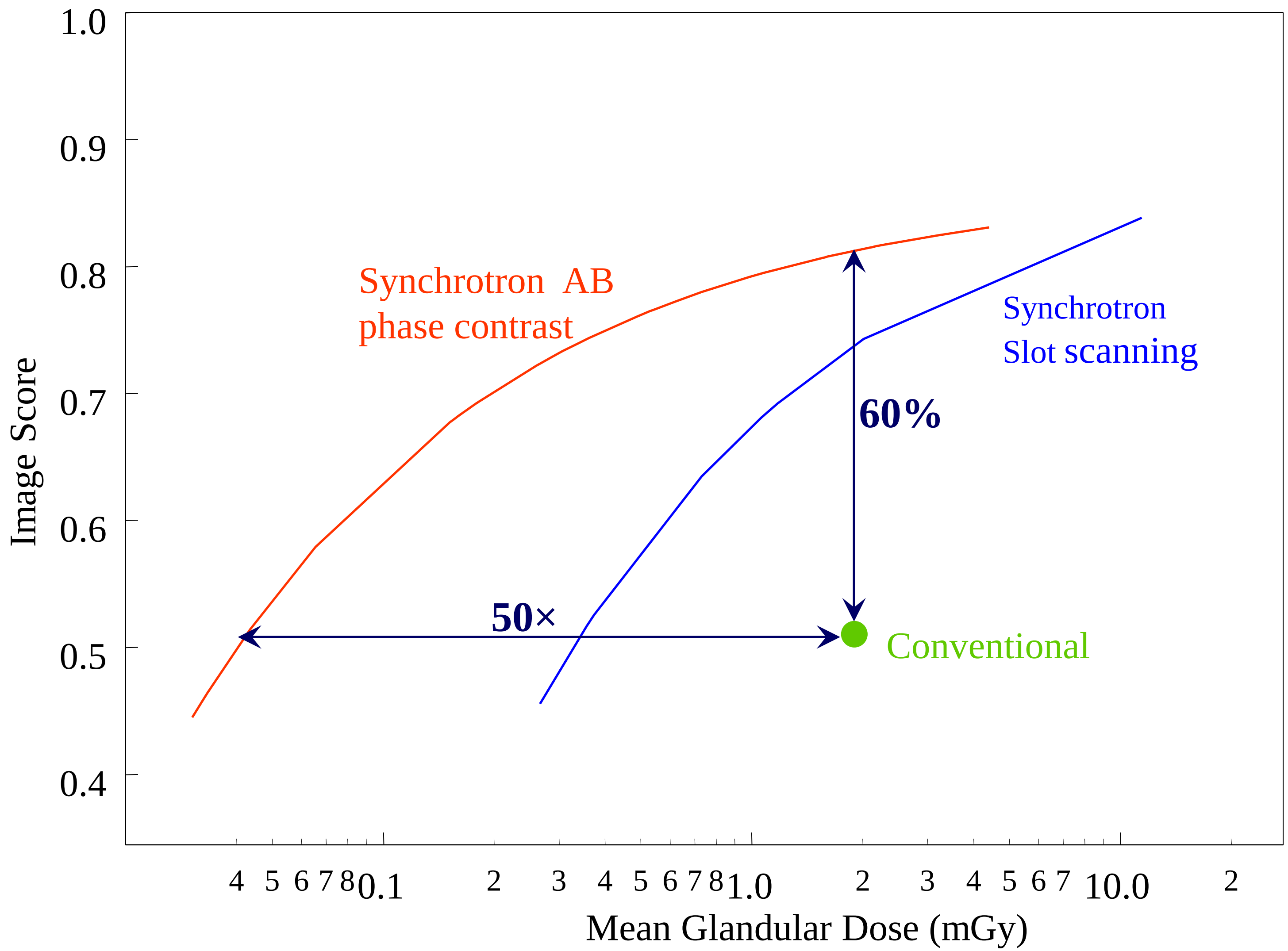


Radiation Dose Resolution Trade-off

- Synchrotrons allow fantastic spatial resolution but……..

$$Dose_{skin} = \frac{2e^{\mu L} SNR_{out}^2}{DQE(f)\mu^2 size_{obj}^4 Contrast_{\mu}^2} E_{\gamma} (\frac{\mu}{\rho})$$

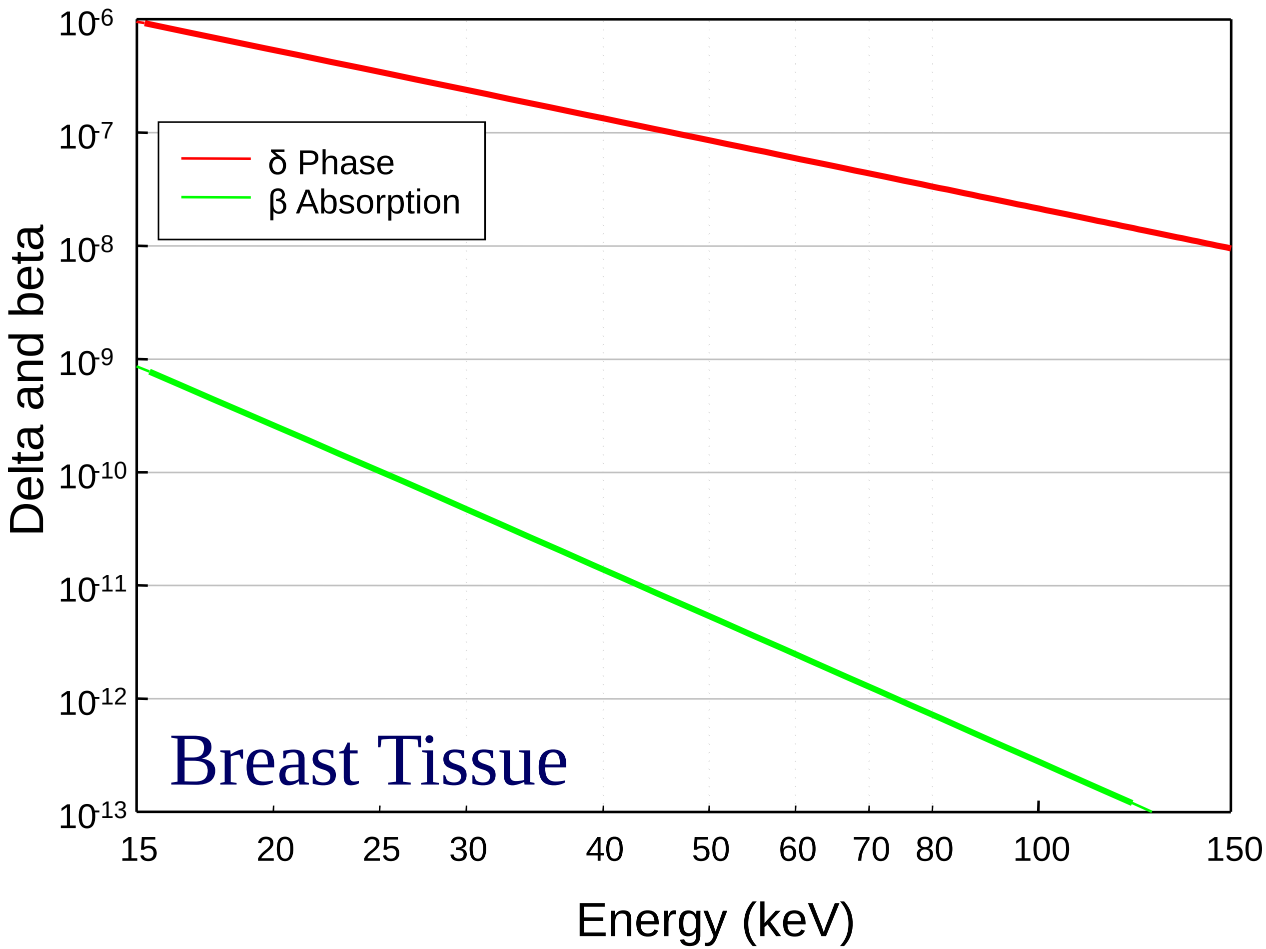
Phase Contrast Dose Advantage



RA Lewis et al SPIE Vol. 4682 (2002) 286-297

Complex Refractive Index

- Coherence properties enable phase contrast
- Contrast arising from phase effects does not require dose to be deposited in the object



Refractive index
$\eta = 1 - \delta - i\beta$

Where β = absorption
δ = phase shift

Nb.
$\delta \sim 1000\ \beta$
$\delta \sim E^{-2}$
$\beta \sim E^{-4}$

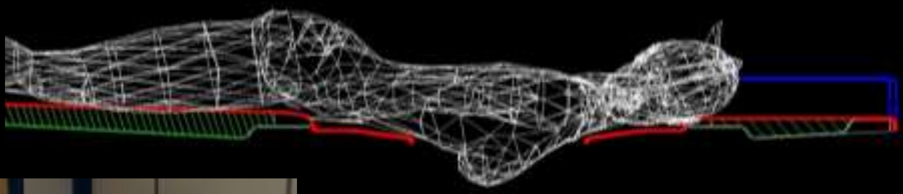
Clinical Mammography at ELETTRA (Trieste, Italy)

Aim of the study: to prospectively evaluate on a limited number of selected patients the diagnostic contribution of SR Phase Contrast mammography in patients with doubtful or suspicious breast lesions identified at the conventional mammography in the Hospital

Phase 1: March 2006 - December 2009 (71 patients)
screen-film system, first protocol for recruitment

Phase 2: in 2012- Image Plate detector, Fuji FCR Capsula XL II

Phase 3: from 2013- digital detector, new recruitment protocol



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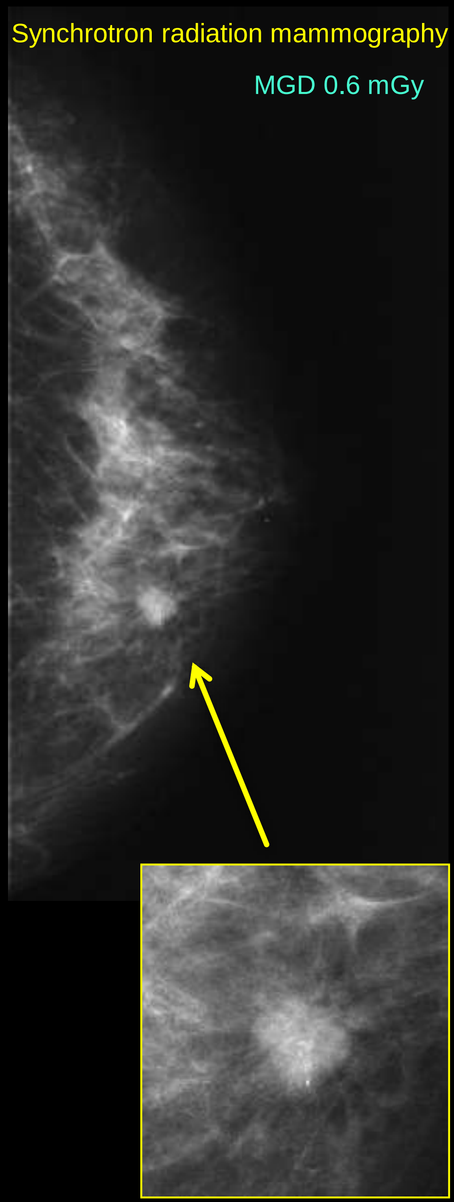
P. Bregant, M.A. Cova, D. Sanabor, E. Quaia, M. Tonutti, F. Zanconati

Clinical Mammography at ELETTRA (Trieste, Italy)



RESULTS

Evaluation of lesions and structure visibility:

comparing mammography with SR and conventional (hospital) mammography

MSR allows a better visualization, both for the lesions and for the glandular tissue

Hospital mammography identified:

21/40 patients with final benign diagnosis

23/29 pt with final malignant diagnosis

MSR identified:

38/40 patient with final benign diagnosis

25/29 patient with final malignancy diagnosis

E. Castelli, M.Tonutti, F.Arfelli, R.Longo, E.Quaia, L.Rigon, D.Sanabor, F. Zanconati, D.Dreossi, A. Abrami, E.Quai, P.Bregant, K.Cesarin, V.Chenda, R.H. Menk, T.Rokvic, A.Vascotto, G.Tromba, MA Cova, *Mammography with Synchrotron Radiation: First Clinical Experience with Phase-Detection Technique*, Radiology, 259 (3), 684-694(2011)

CT and Radiography Problems

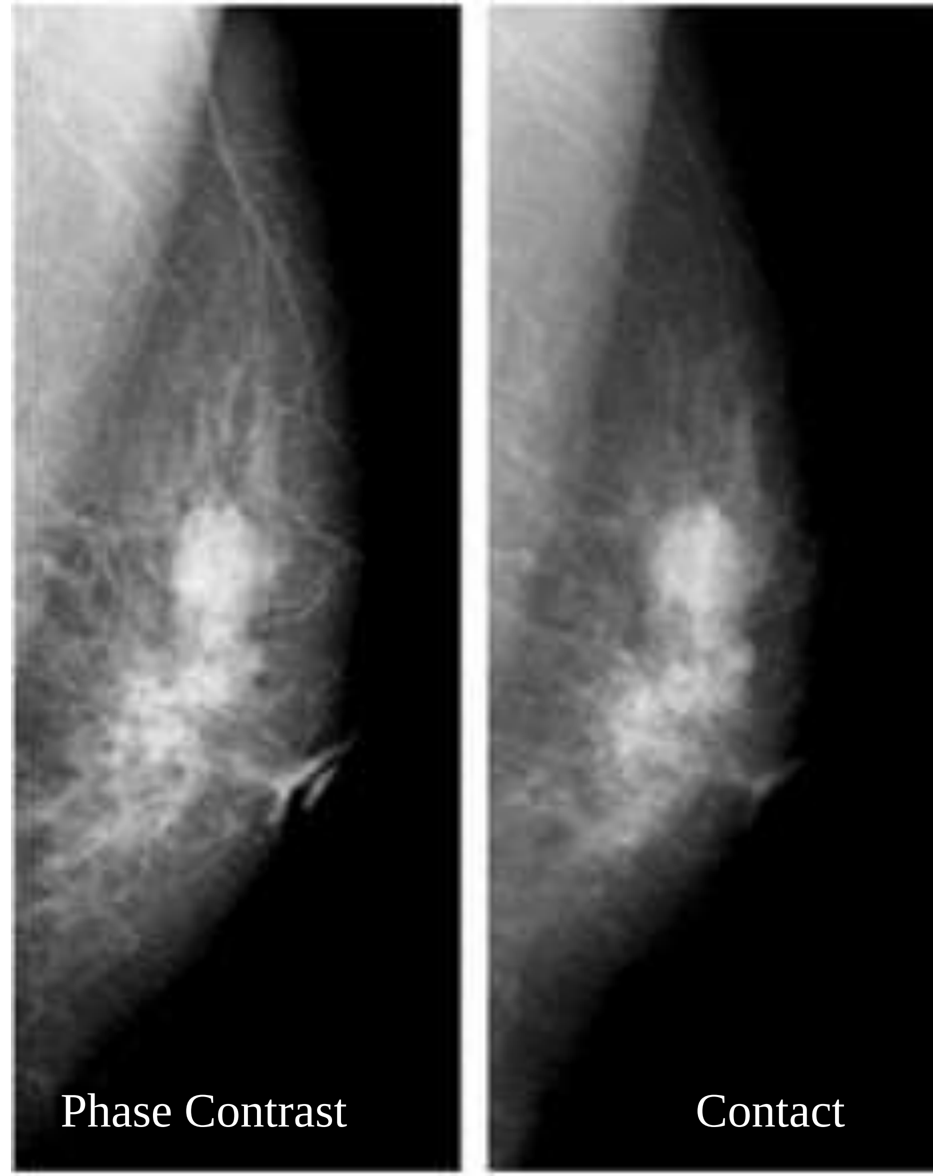
- X-ray Dose
  - Phase Contrast Helps. Synchrotron easy. Gratings?
- Scatter
  - Greatly reduced by slot scanning. Both conventional and synchrotron can use this.
- Beam Hardening
  - Eliminated by monochromatic radiation. Synchrotron only
- Cone Beam Artefacts
  - Eliminated by parallel beam. Synchrotron only.

Synchrotron Medical Imaging

- Synchrotron Medical Imaging
  - ✓ Fantastic spatial resolution
  - ✓ Reasonable scan times
  - ✘ Uses ionising radiation
  - ✘ Very limited access
  - ✘ Extremely expensive
- Synchrotrons are not currently suitable for "routine" medical procedures

Phase Contrast in the Clinic

Konica Minolta REGIUS PureView



Development of standing type machine

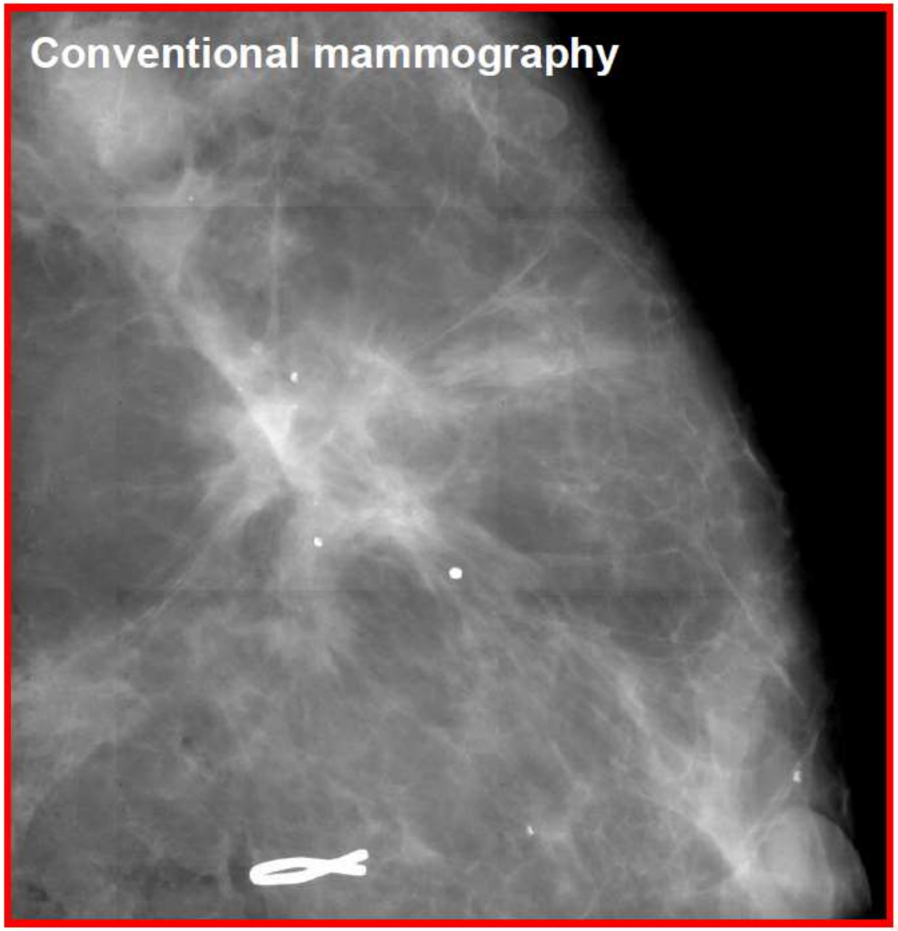
second finger

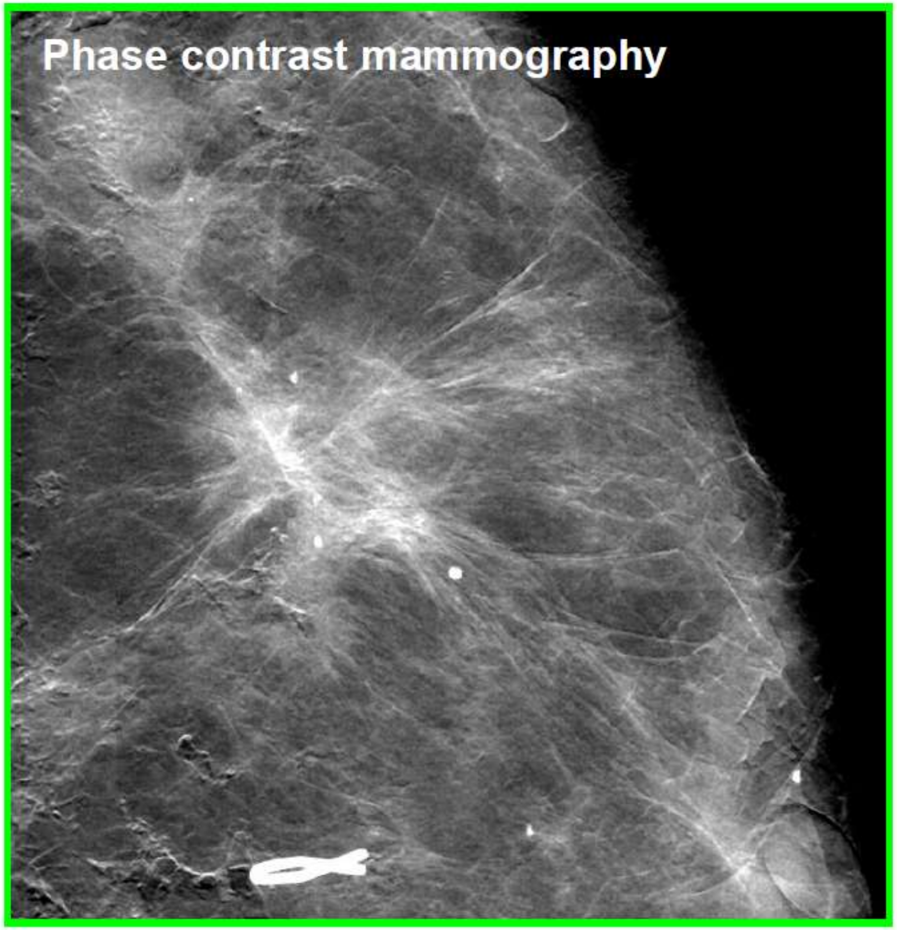
first finger

Measurement : 32 sec
X-ray exposure : 19 sec
Skin dose : **5 mGy**

Junji Tanaka, Masabumi Nagashima, Kazuhiro Kido, Yoshihide Hoshino, Junko Kiyohara, Chiho Makifuchi, Satoshi Nishino, Sumiya Nagatsuka, and Atsushi Momose, “Cadaveric and in vivo human joint imaging based on differential phase contrast by X-ray Talbot-Lau interferometry”, Z. Med. Physk, *submitted*.

Enhanced *spiculations* visibility





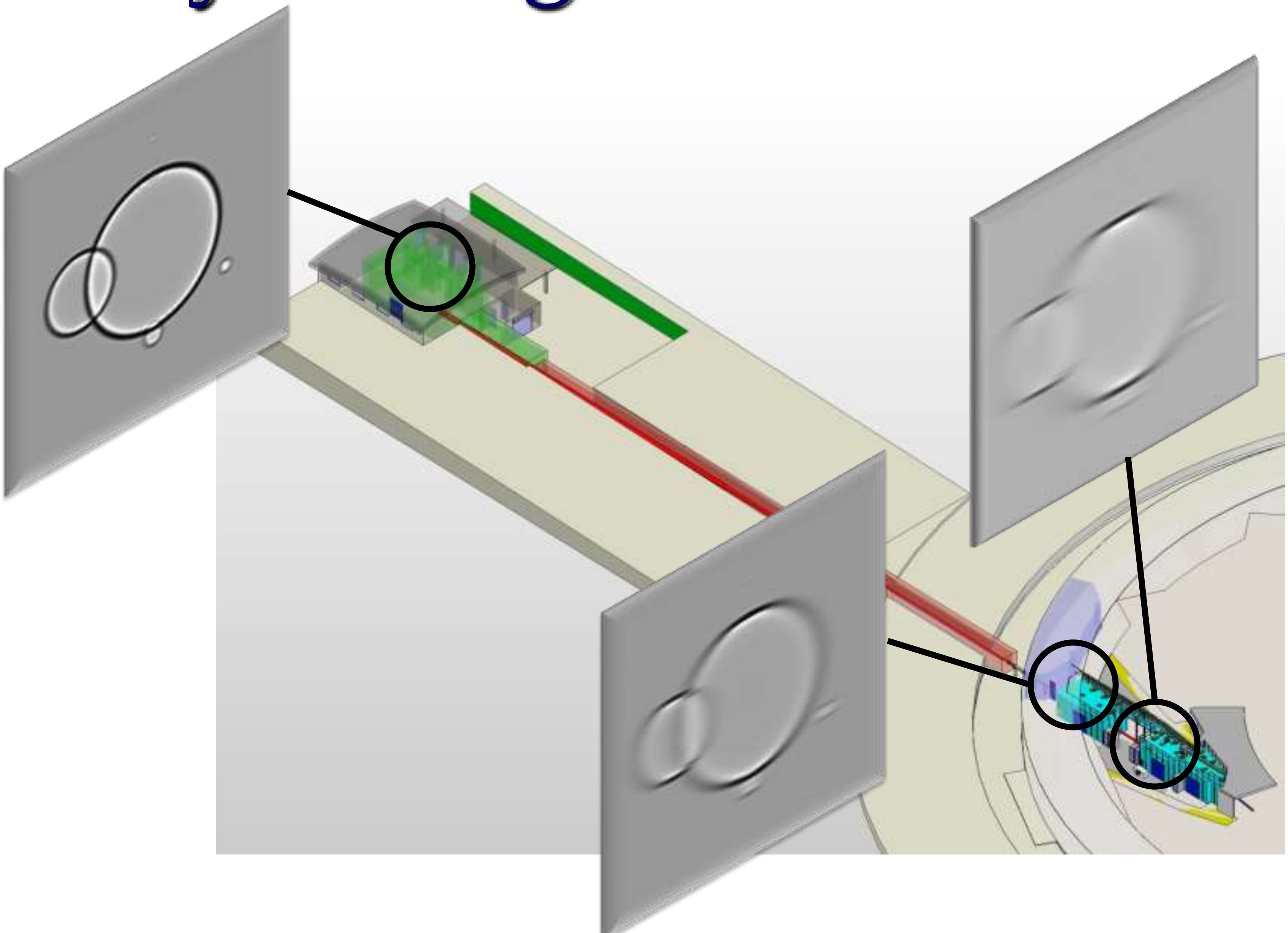
Z. Wang, XNPIG2012

Birth: An amazing event

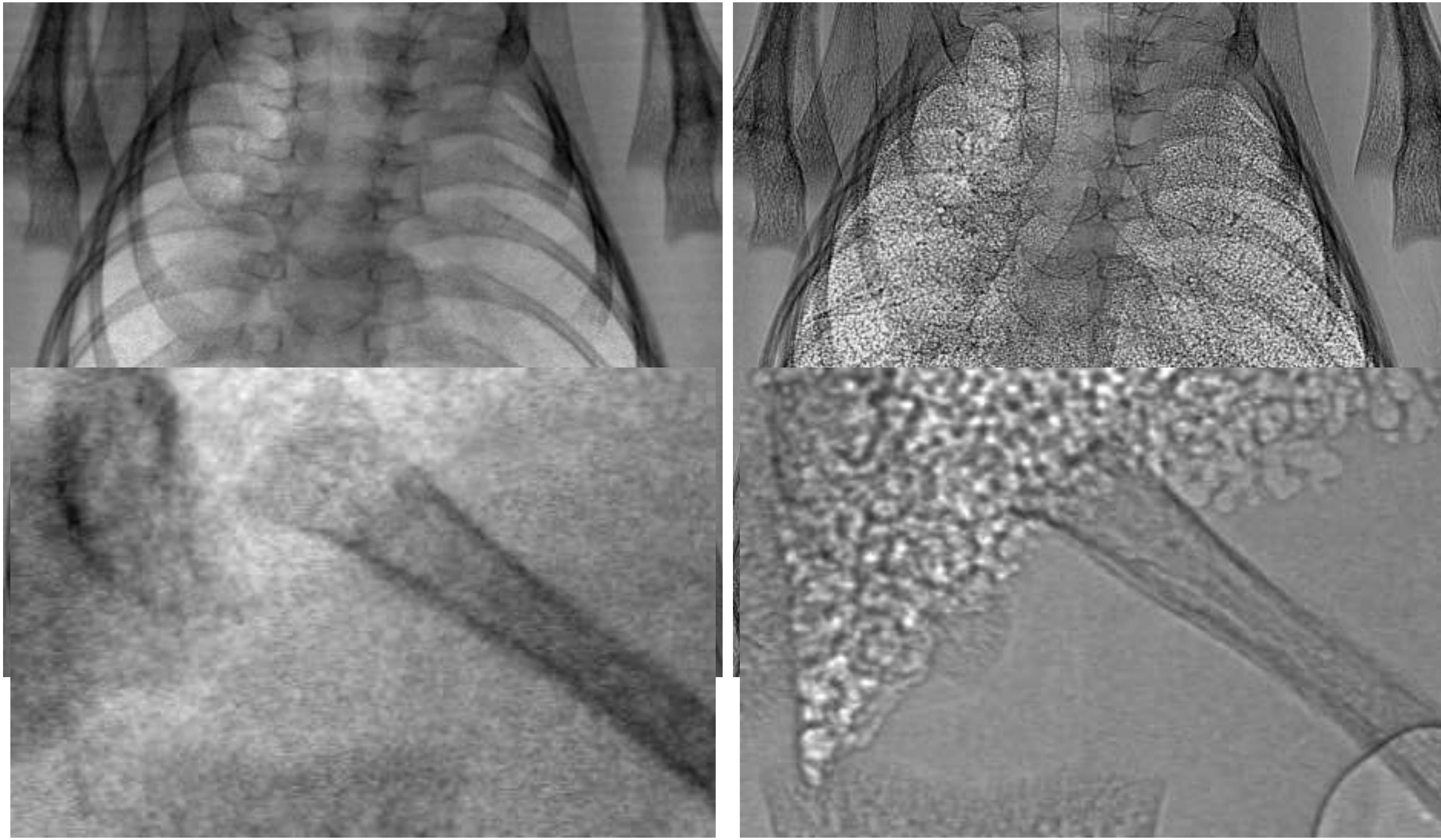
- In utero lungs are full of liquid
- At birth lungs fill with air
- The transition is poorly understood
- Preterm and caesarean section infants can have major problems and often need to be ventilated
- We don’t know how to best ventilate and sometimes ventilation injures the lung

SPring-8 - Super Photon ring-8GeV

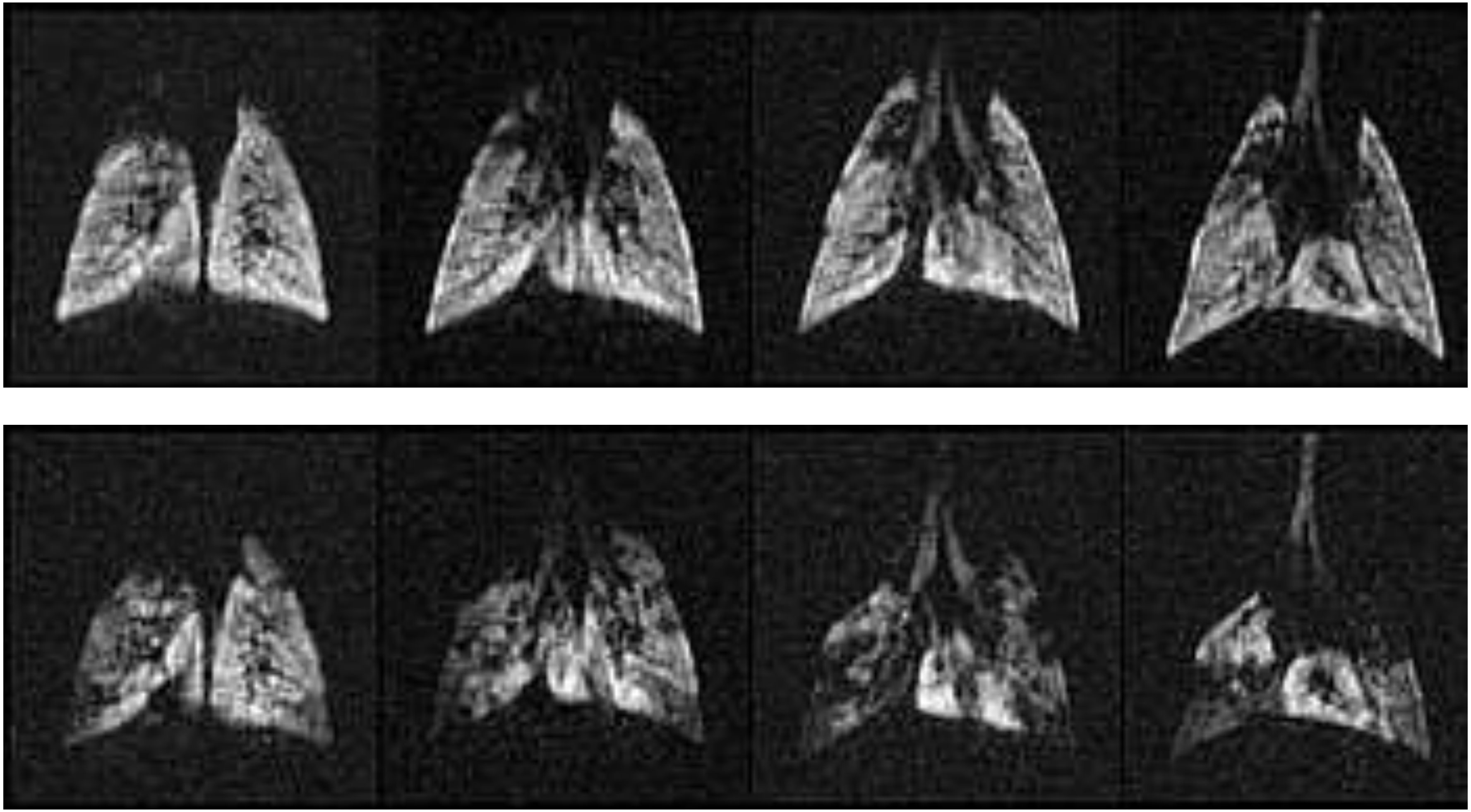
Why a Long Beamline?



Rabbit Lung



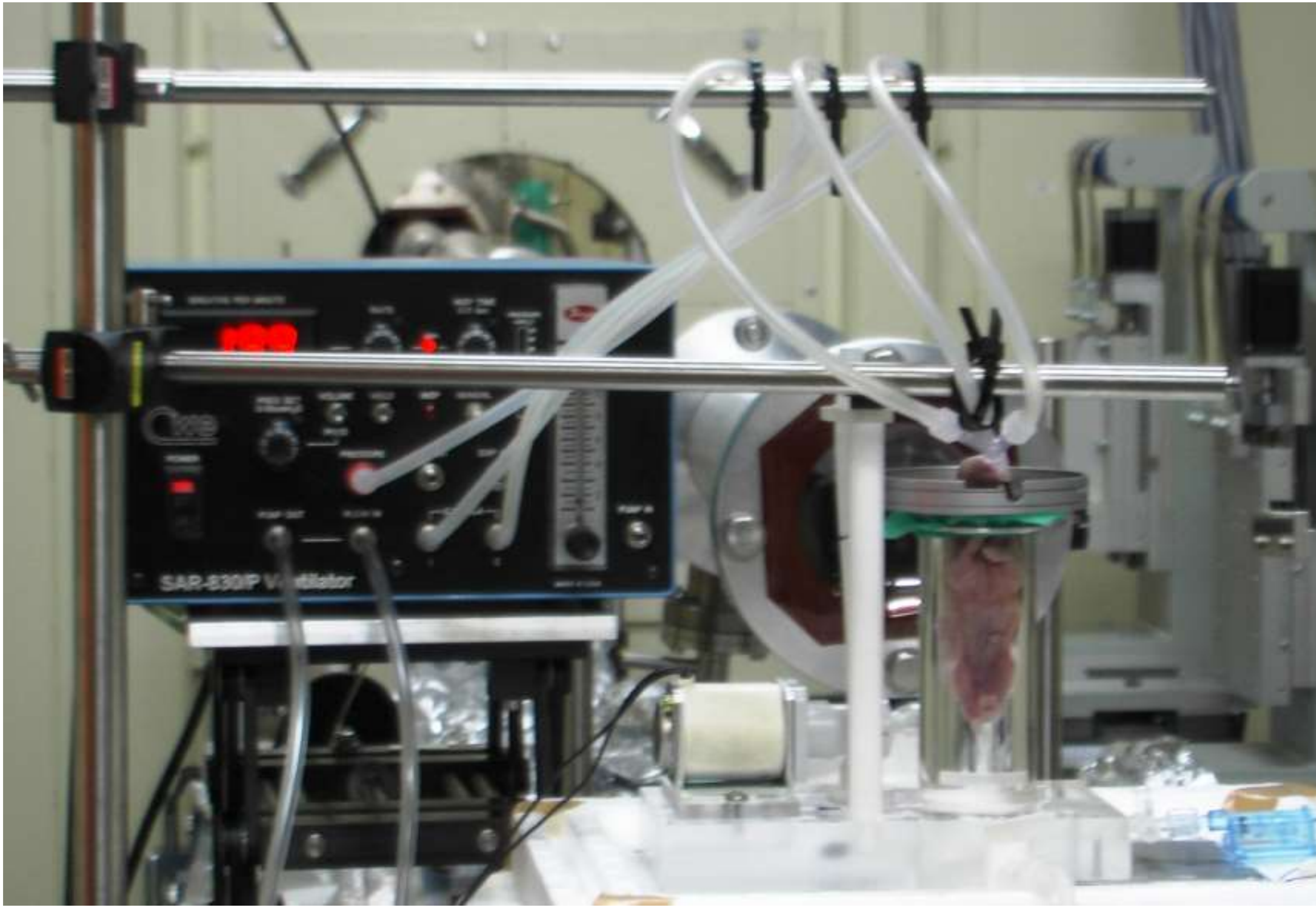
MRI State of the Art



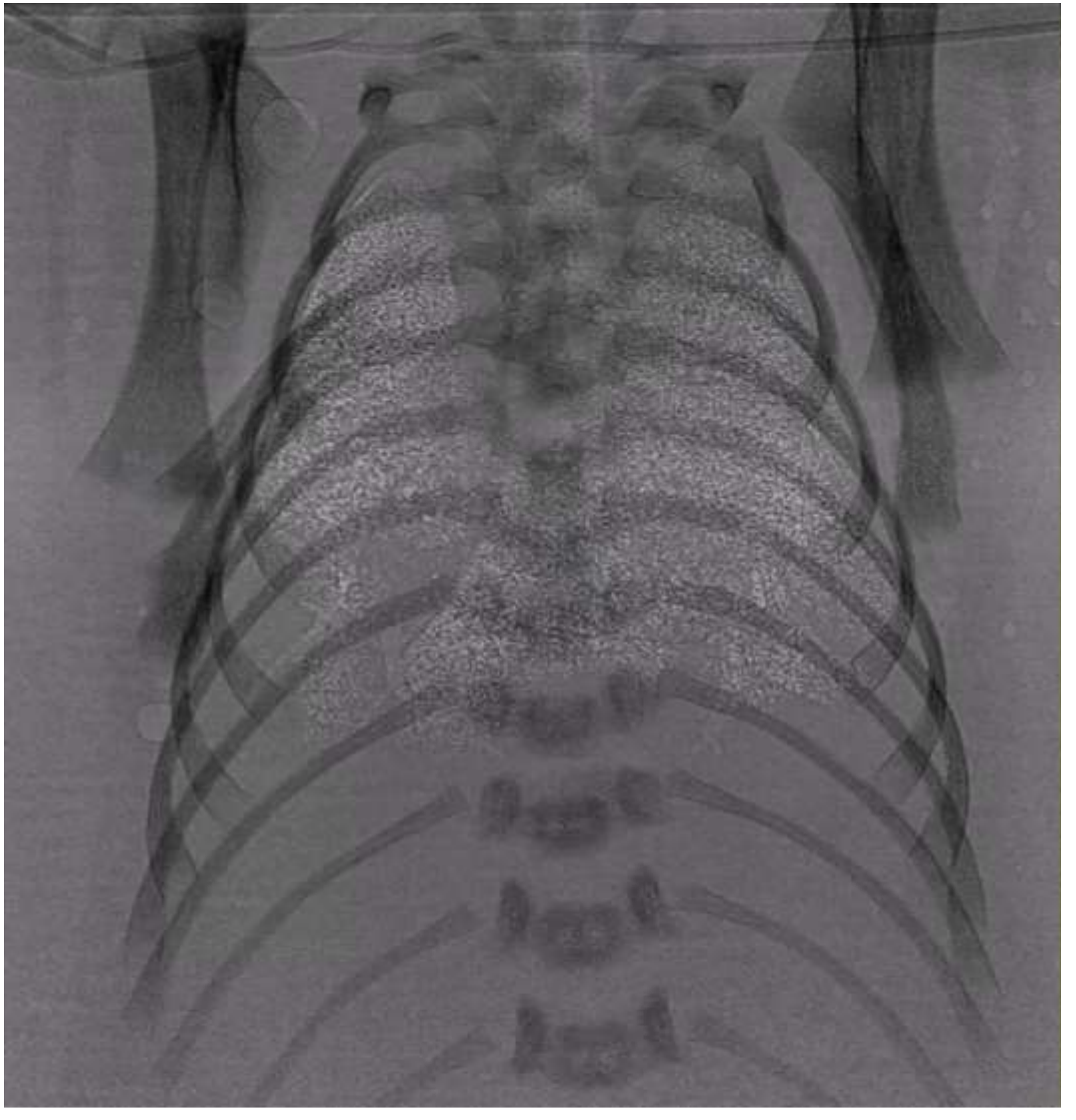
Bronchoconstriction induced by metacholine

Rabbit Pup Lung Imaging - Delivery

Artificial Ventilation



Post Mortem Artificial Ventilation



RA Lewis et al Phys. Med. Biol. **50,** 5031
S. Hooper et al FASEB **21**, 3330 (2007)

UNIVERSITY OF SASKATCHEWAN MONASH University

Phase Retrieval: Single Image

- Approximate ‘contact’ intensity from Beer’s Law

$$I(\mathbf{r}_\perp, z=0) = I_O \exp(-\mu T(\mathbf{r}_\perp))$$

- Approximate ‘contact’ phase by

$$\phi(\mathbf{r}_\perp, z=0) = -\frac{2\pi}{\lambda}\delta T(\mathbf{r}_\perp)$$

- Use Transport-of-Intensity Equation (TIE)

$$\nabla_\perp \cdot (I(\mathbf{r}_\perp, z)\nabla_\perp \phi(\mathbf{r}_\perp, z)) = -\frac{2\pi}{\lambda}\frac{\partial}{\partial z} I(\mathbf{r}_\perp, z)$$

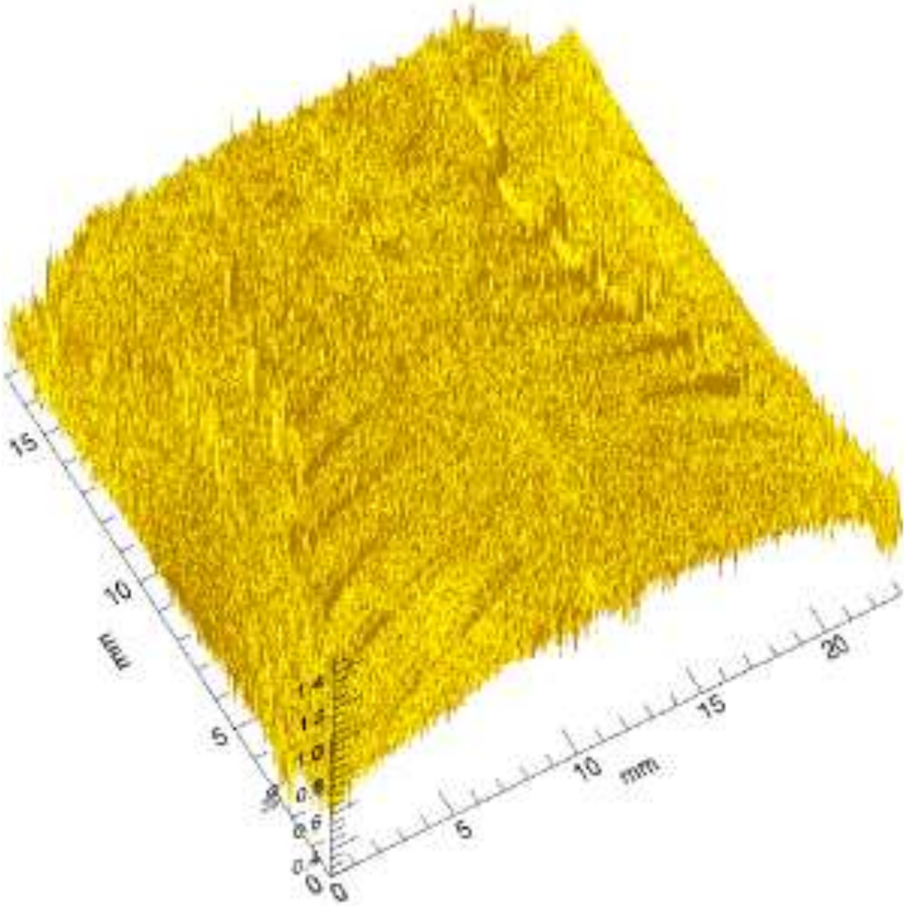
- Solve for object’s projected thickness using Fourier Derivative Theorem

$$T(\mathbf{r}_\perp) = -\frac{1}{\mu}\ln\left(\mathbf{F}^{-1}\left\{\mu\frac{\mathbf{F}\left\{M^2 I(M\mathbf{r}_\perp, z=R_2)\right\}/I_O}{MR_2\delta|\mathbf{k}_\perp|^2+\mu}\right\}\right)$$

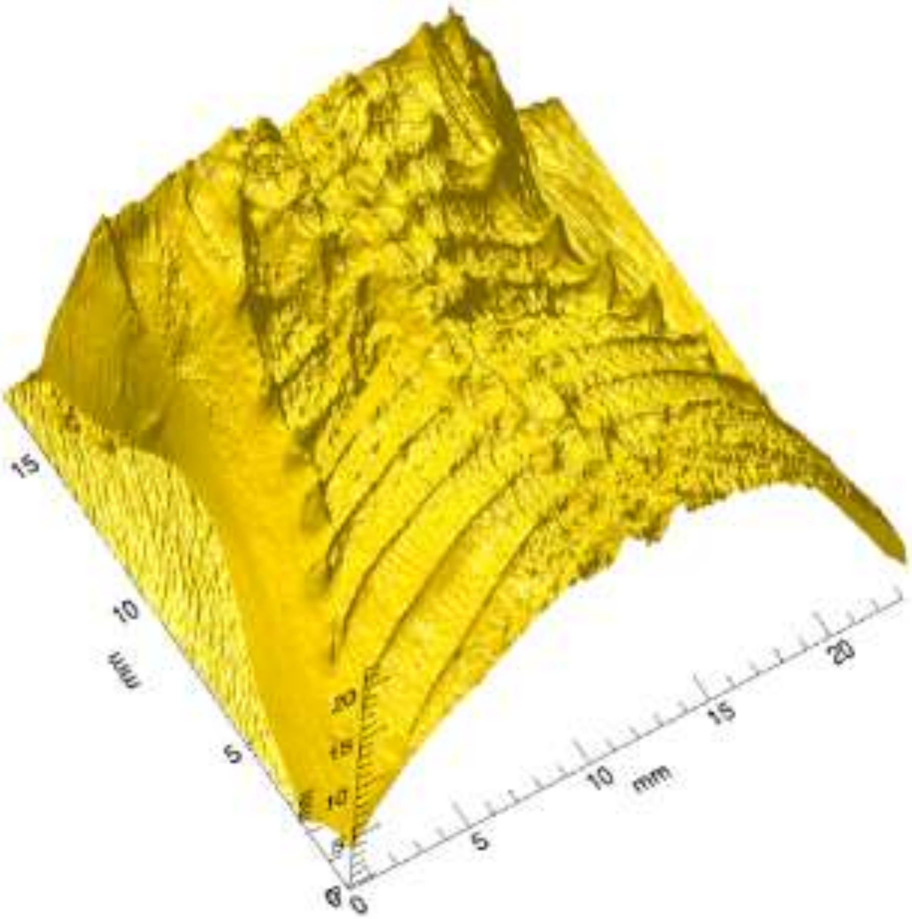
Paganin, D et al., Journal of Microscopy, Vol. 206 Pt 1 April 2002, pp. 33-40

Phase to Projected Thickness

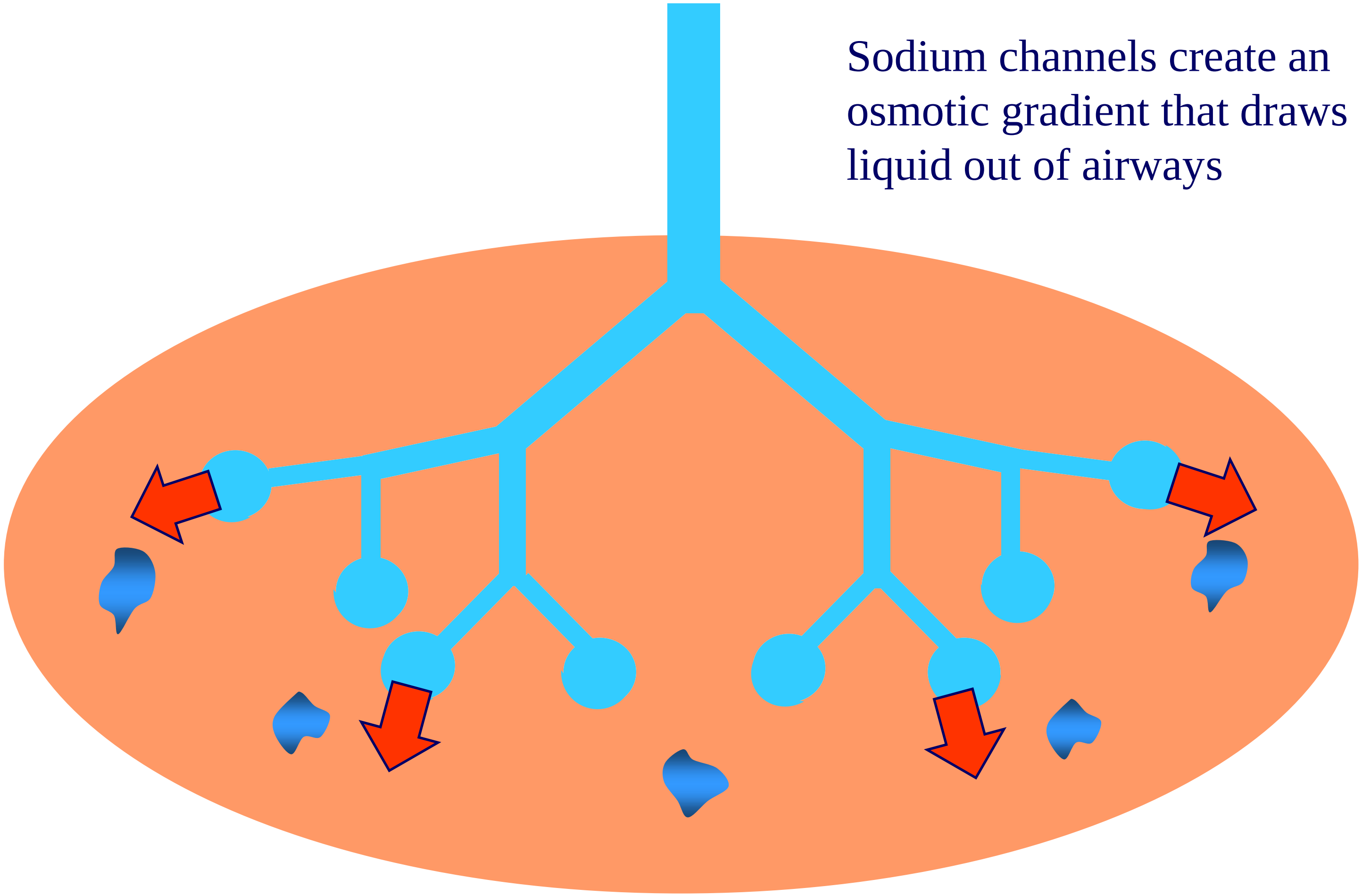
Phase image R_2=4.26m, E=33keV



Projected thickness

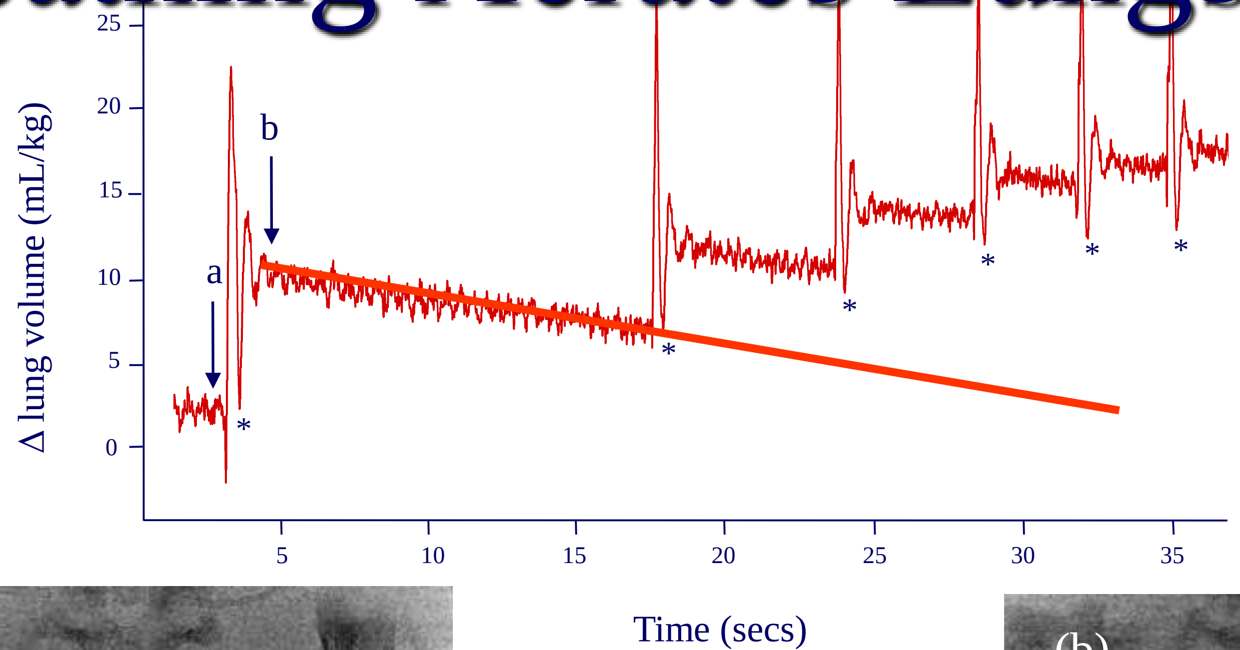


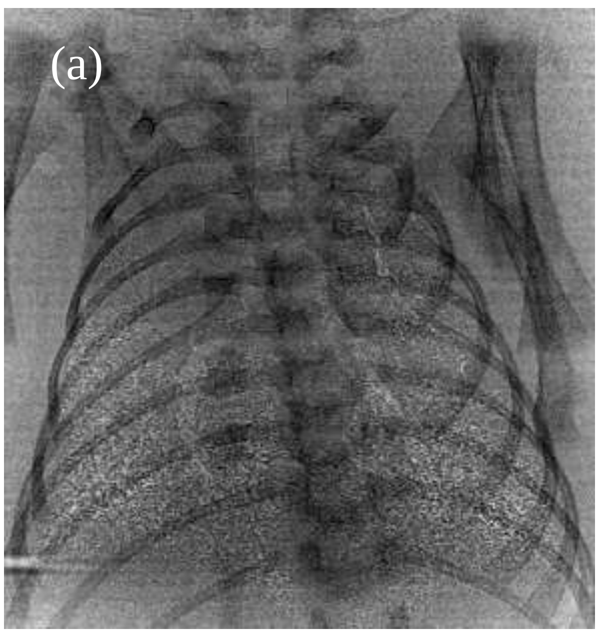
Lung aeration: Airway liquid clearance

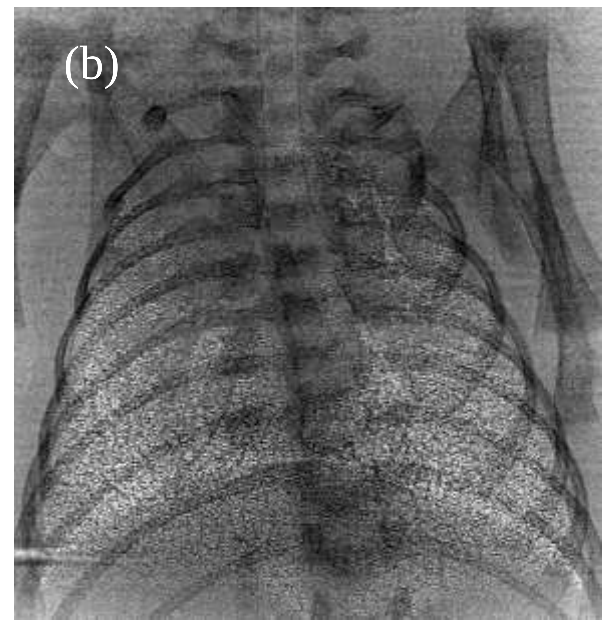


Sodium channels create an osmotic gradient that draws liquid out of airways

Breathing Aerates Lungs







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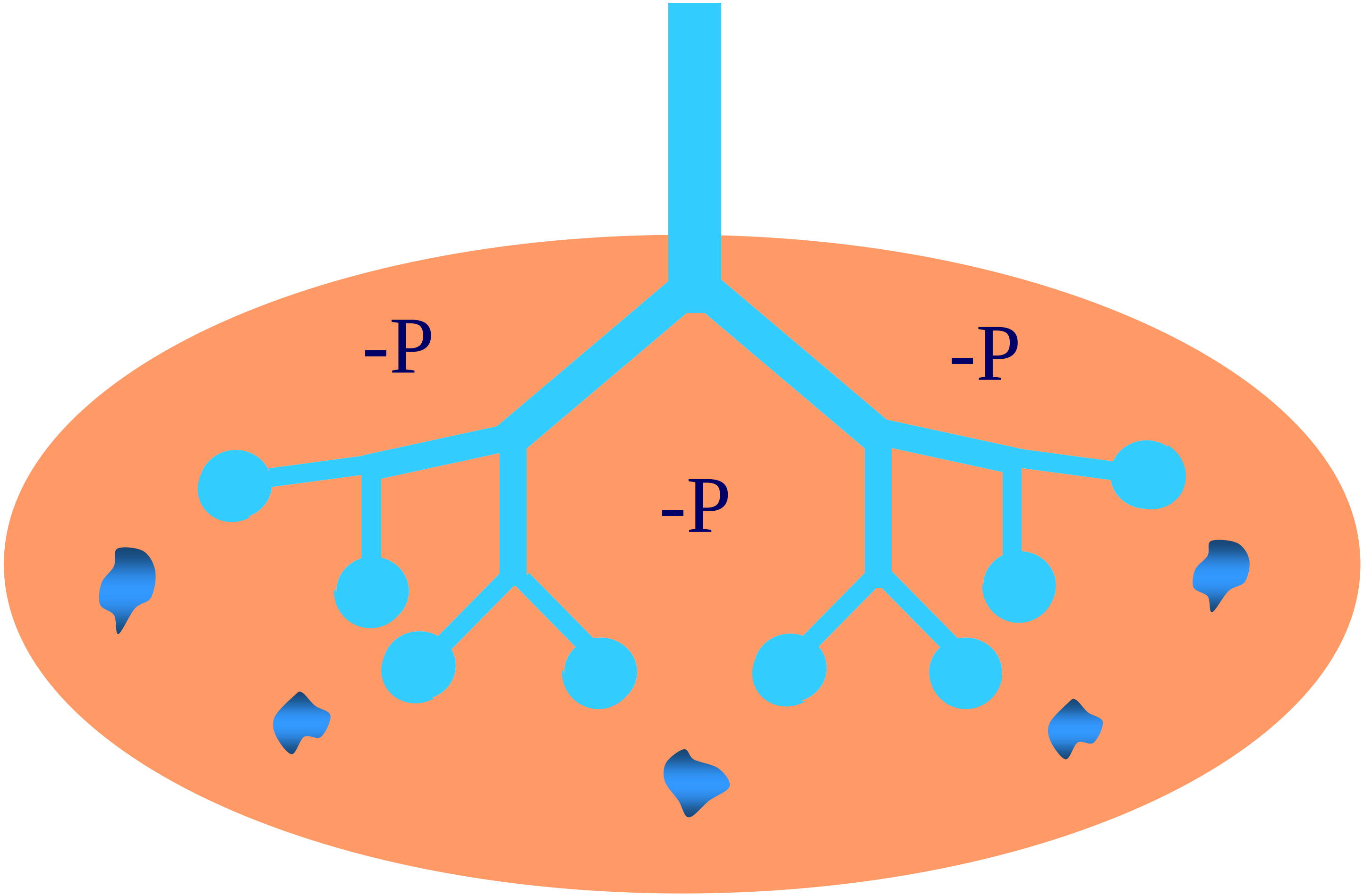
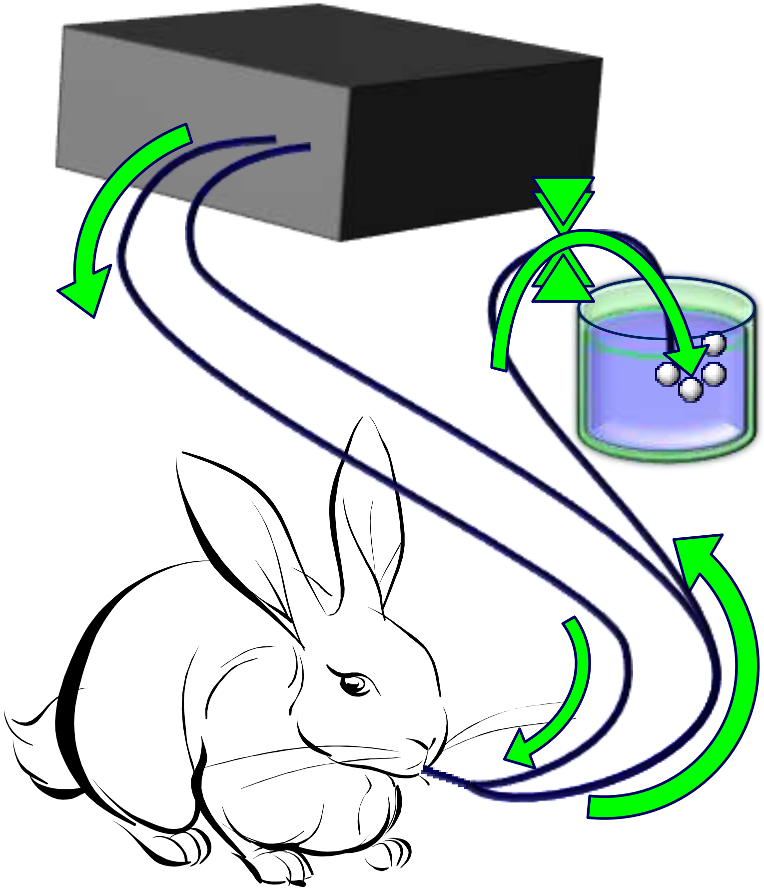
Lung aeration: Airway liquid clearance

Inspiration forces liquid out of airways

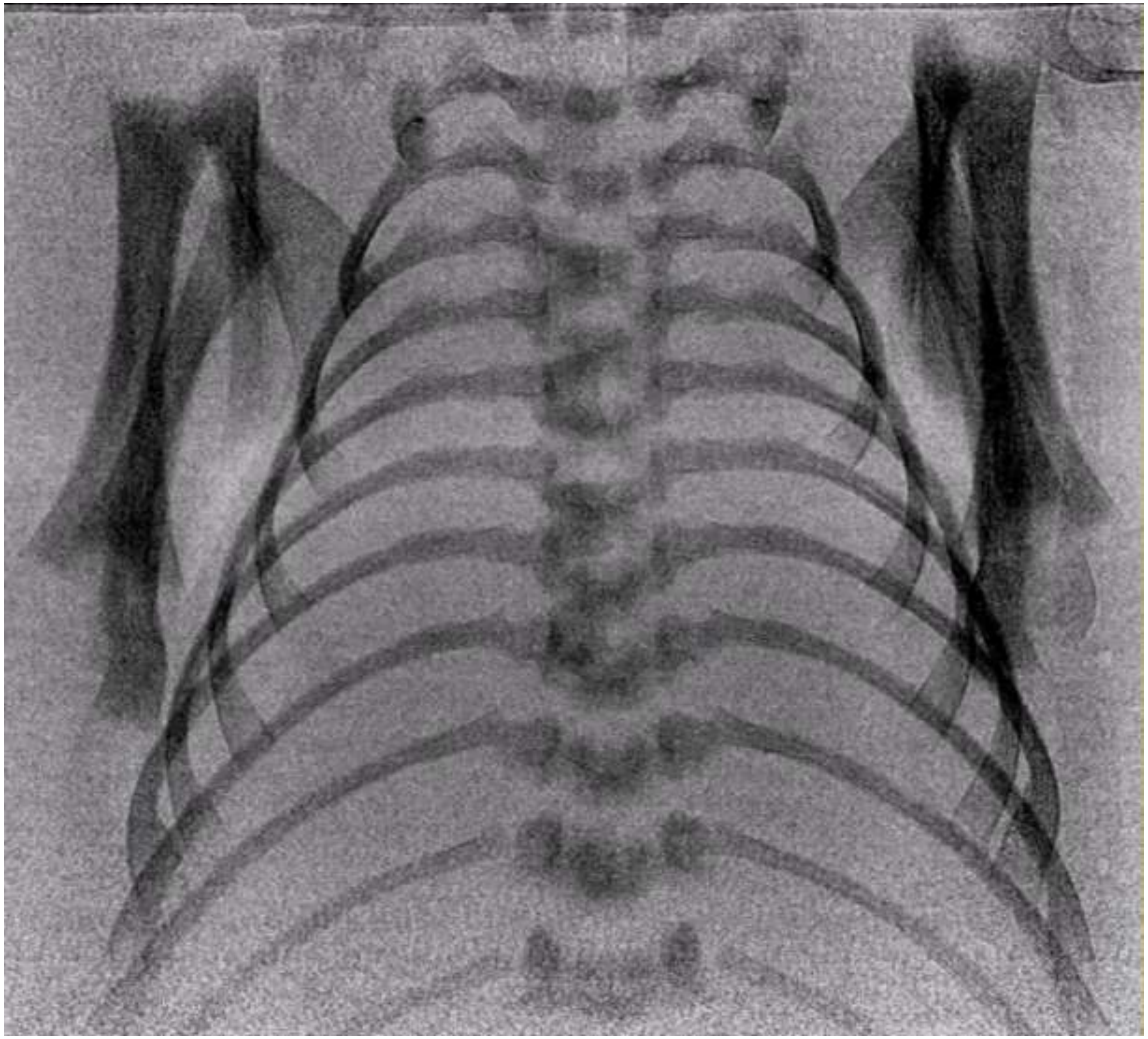


Medical Relevance

- Respiratory Ventilation
- Positive End Expiratory Pressure (PEEP) used to be excluded from international resuscitation guidelines for ventilating infants due to lack of evidence
- It is now recommended as a direct consequence of this work

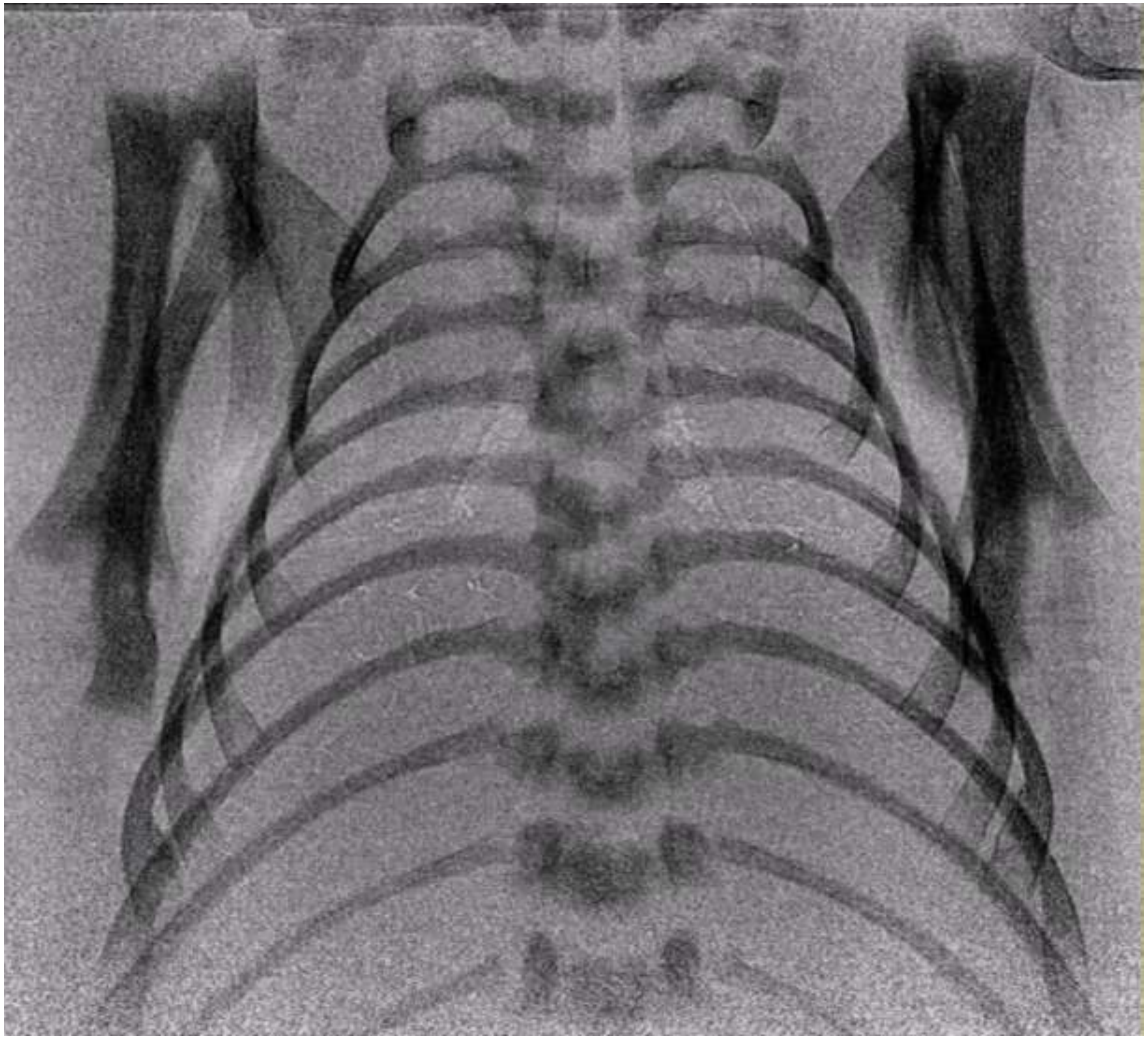


Rabbit Pup: No PEEP



RA Lewis et al Phys. Med. Biol. **50,** 5031
S. Hooper et al FASEB **21**, 3330 (2007)

Rabbit Pup: With PEEP



Te Pas et al Pediatric Research **65**(5), 537-541 2009
S. Hooper et al FASEB **21**, 3330 (2007)

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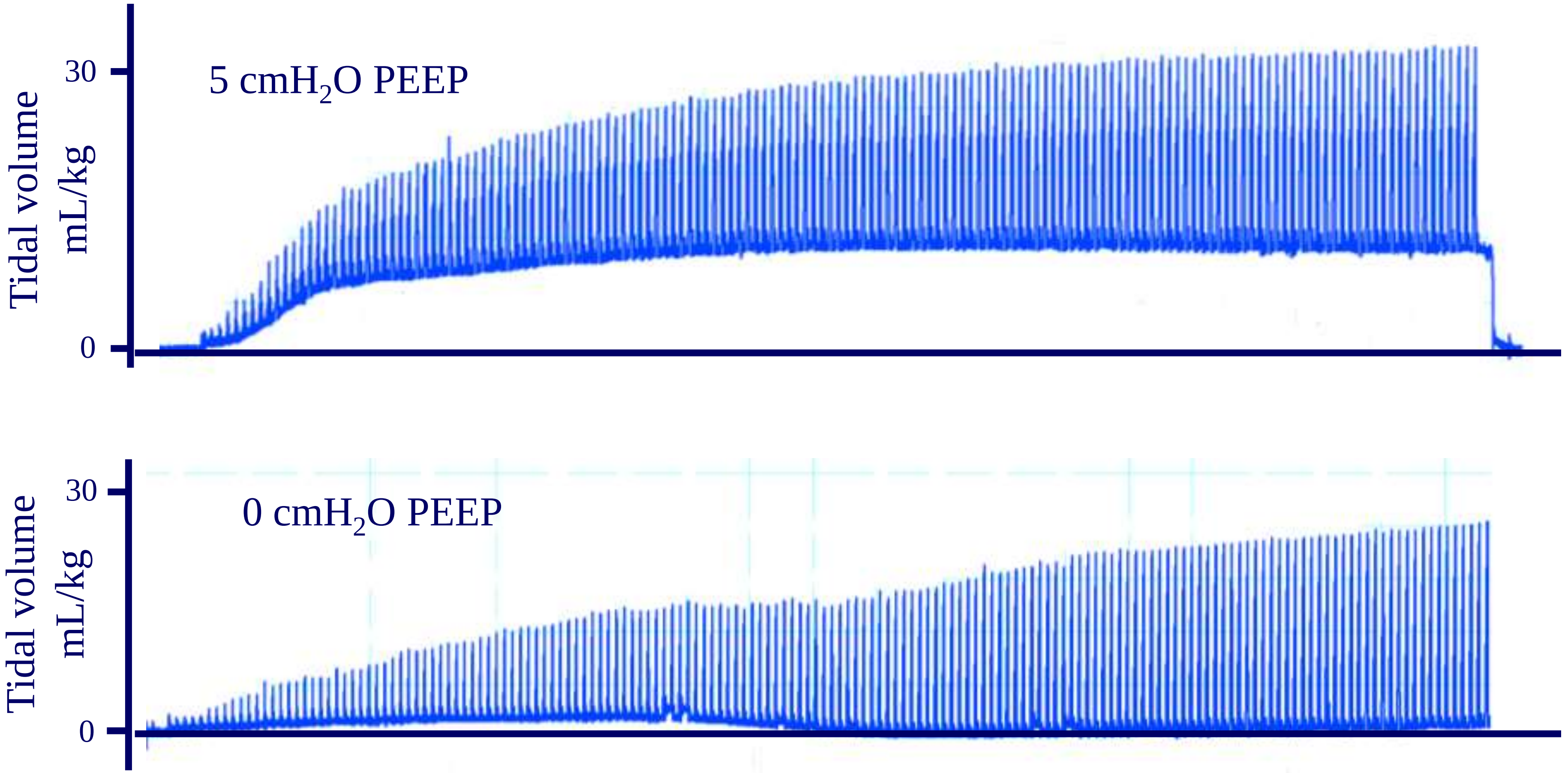
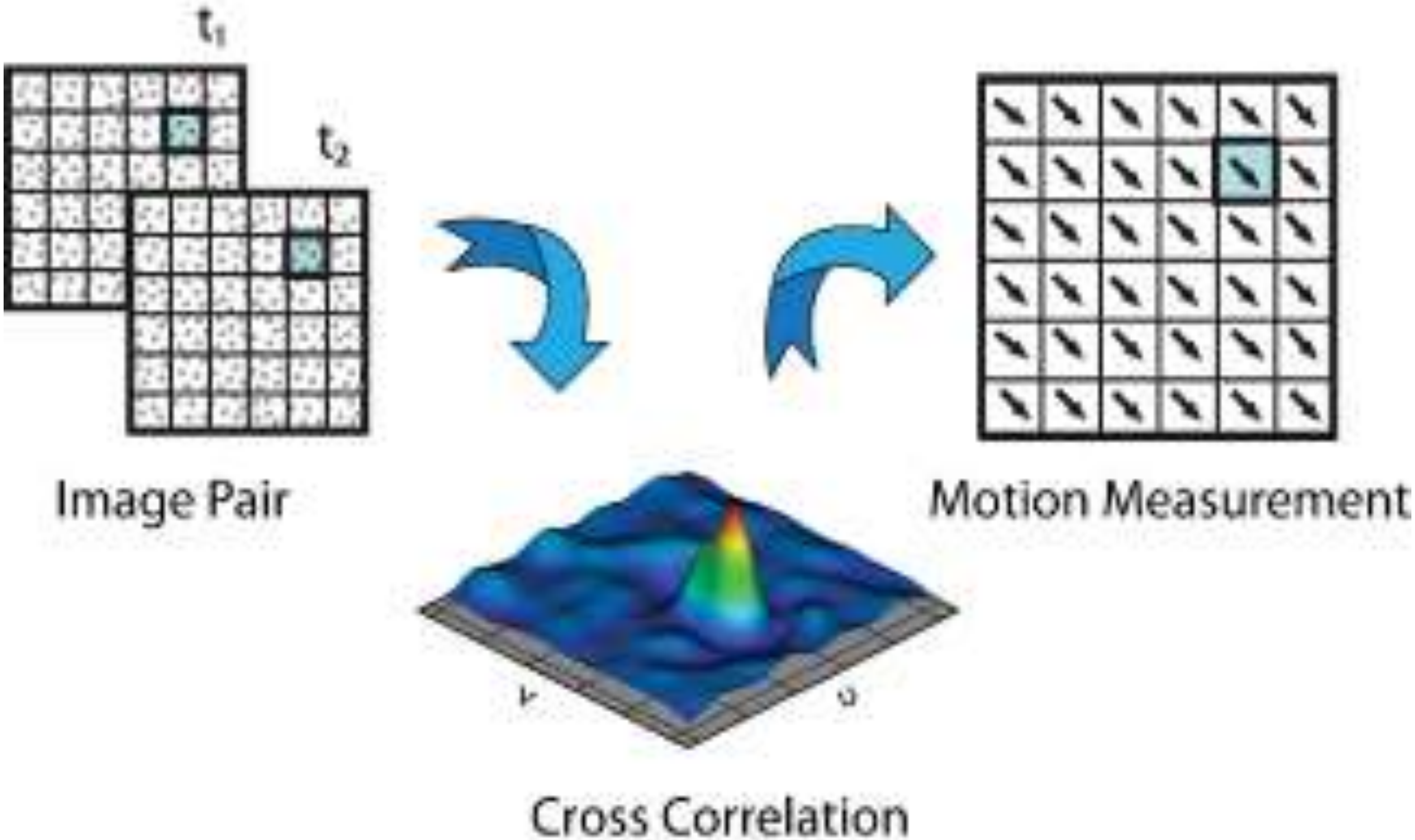
Effect of PEEP in Ventilated Preterm Rabbits

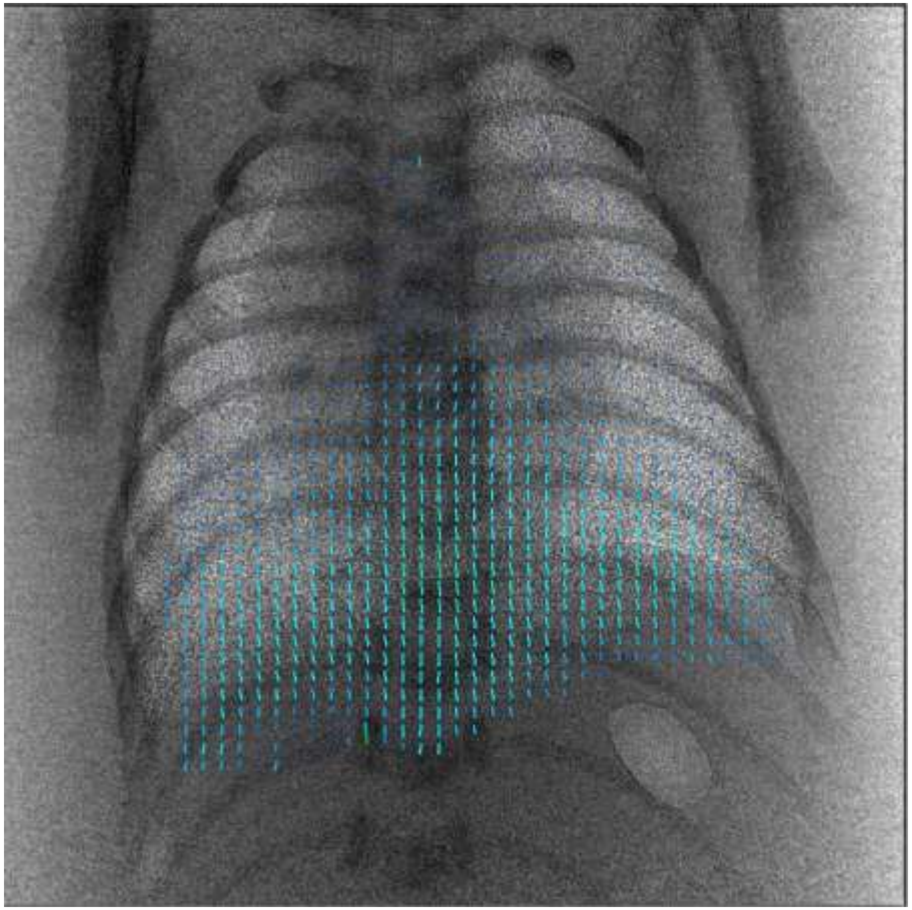


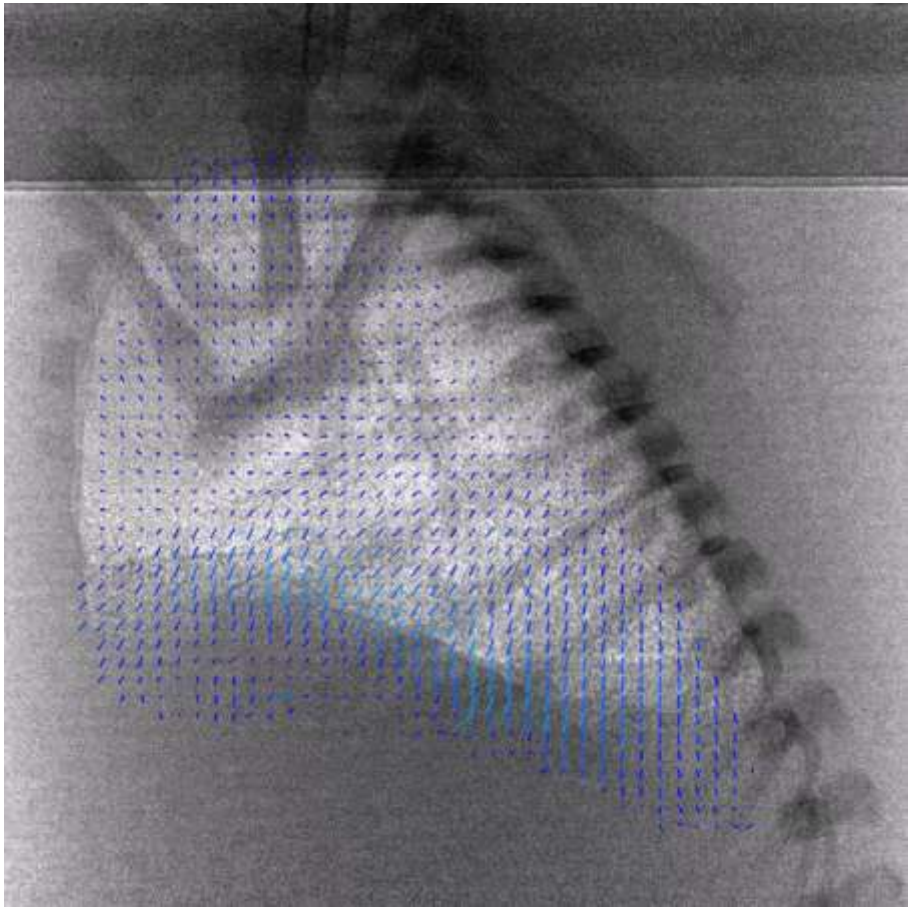
Measuring Lung Motion

- Particle Image Velocimetry detects speed & direction of particle (lung) motion



Particle Image Velocimetry



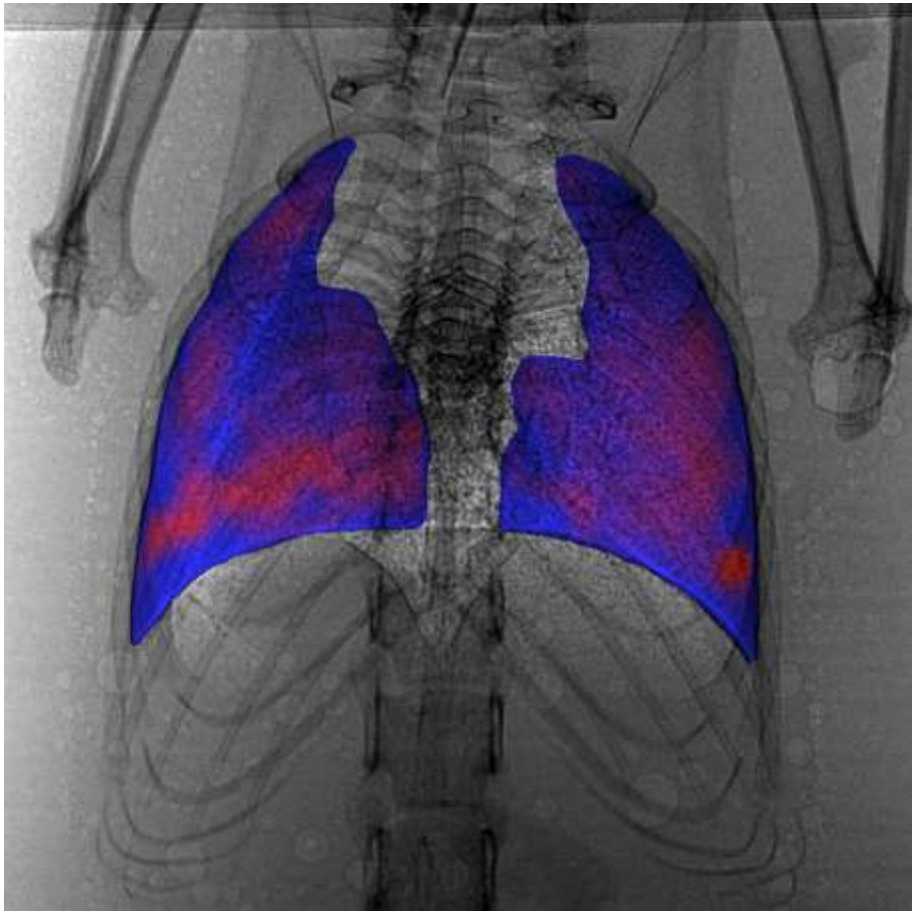


A. Fouras, et al

Disease Detection

Plots of regional compliance, calculated from motion maps in mouse lungs

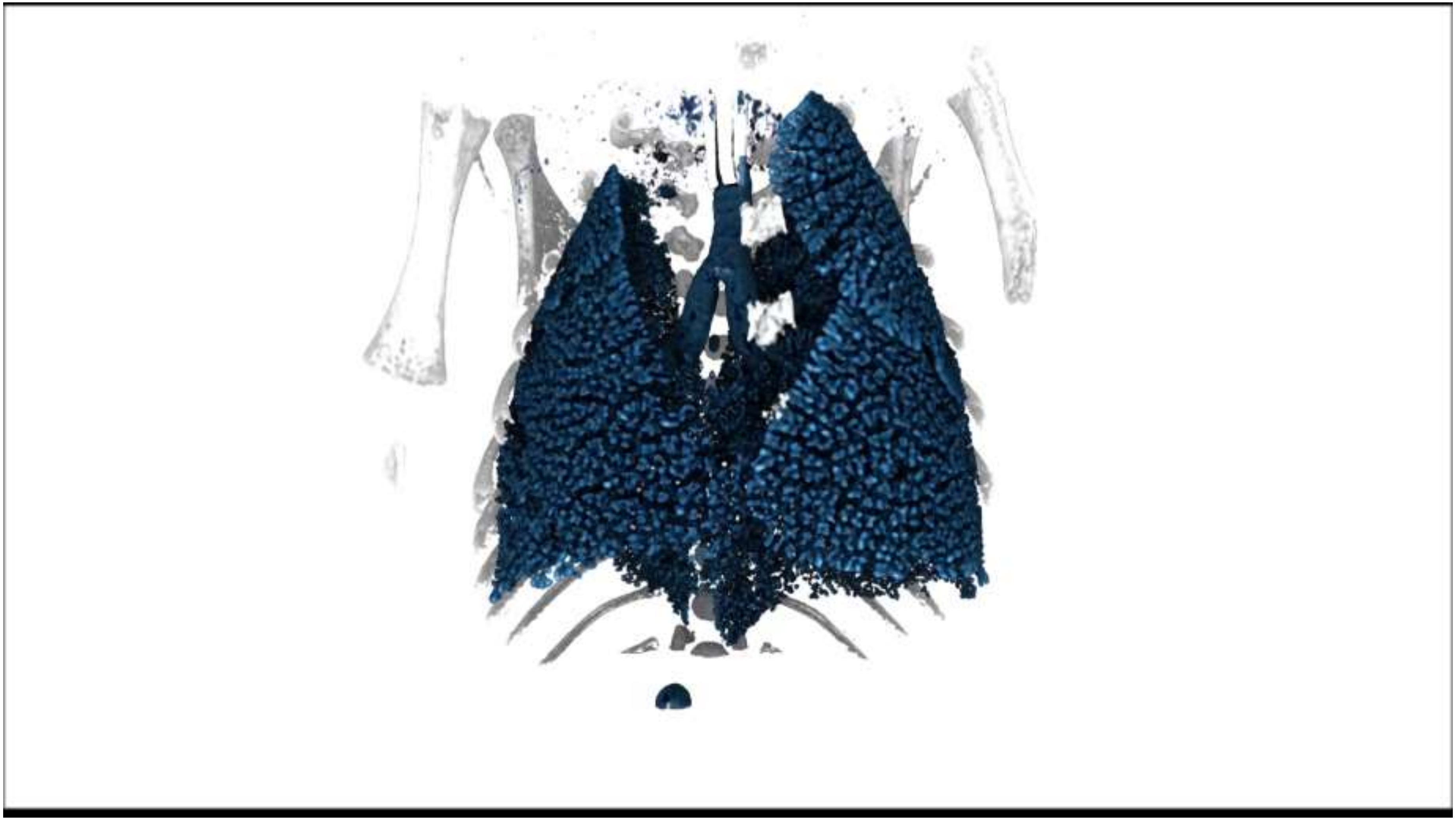
Healthy Lung, showing uniform compliance



Fibrotic lung, showing regional differentiation of compliance

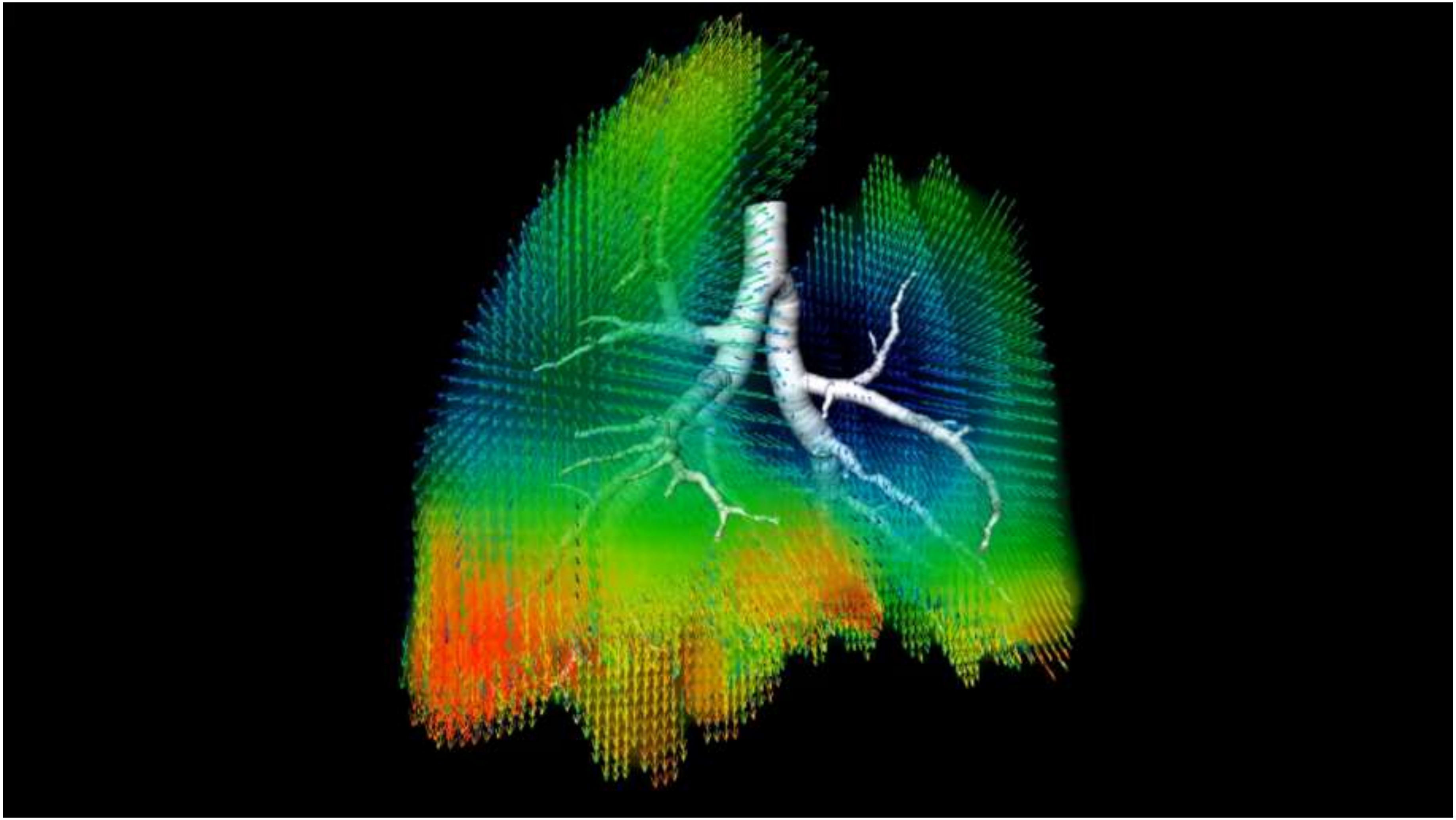
A. Fouras, S Dubsky et al

Whole Breath Lung Morphology



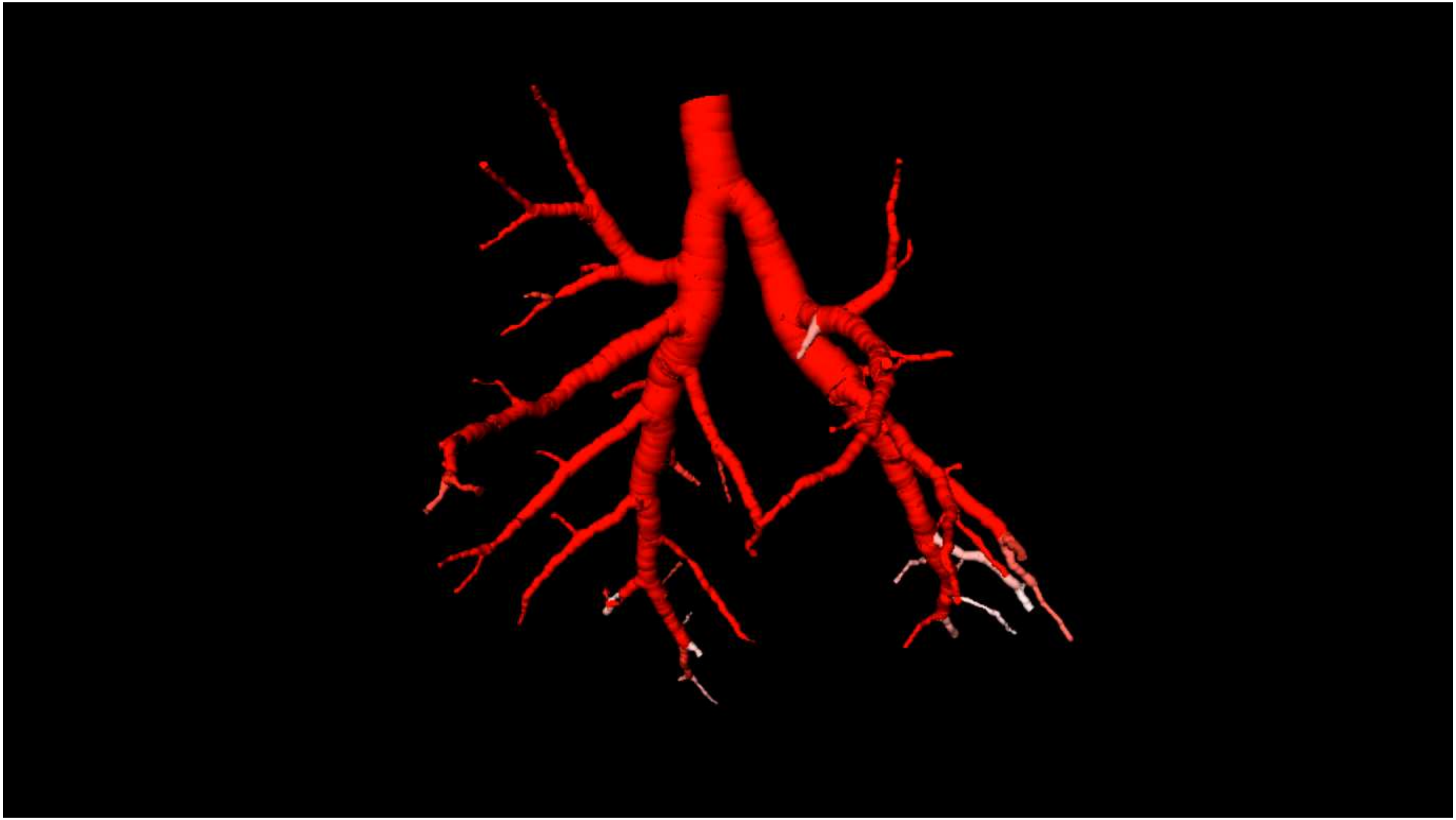
S Dubsky, A Fouras et al

4D PIV

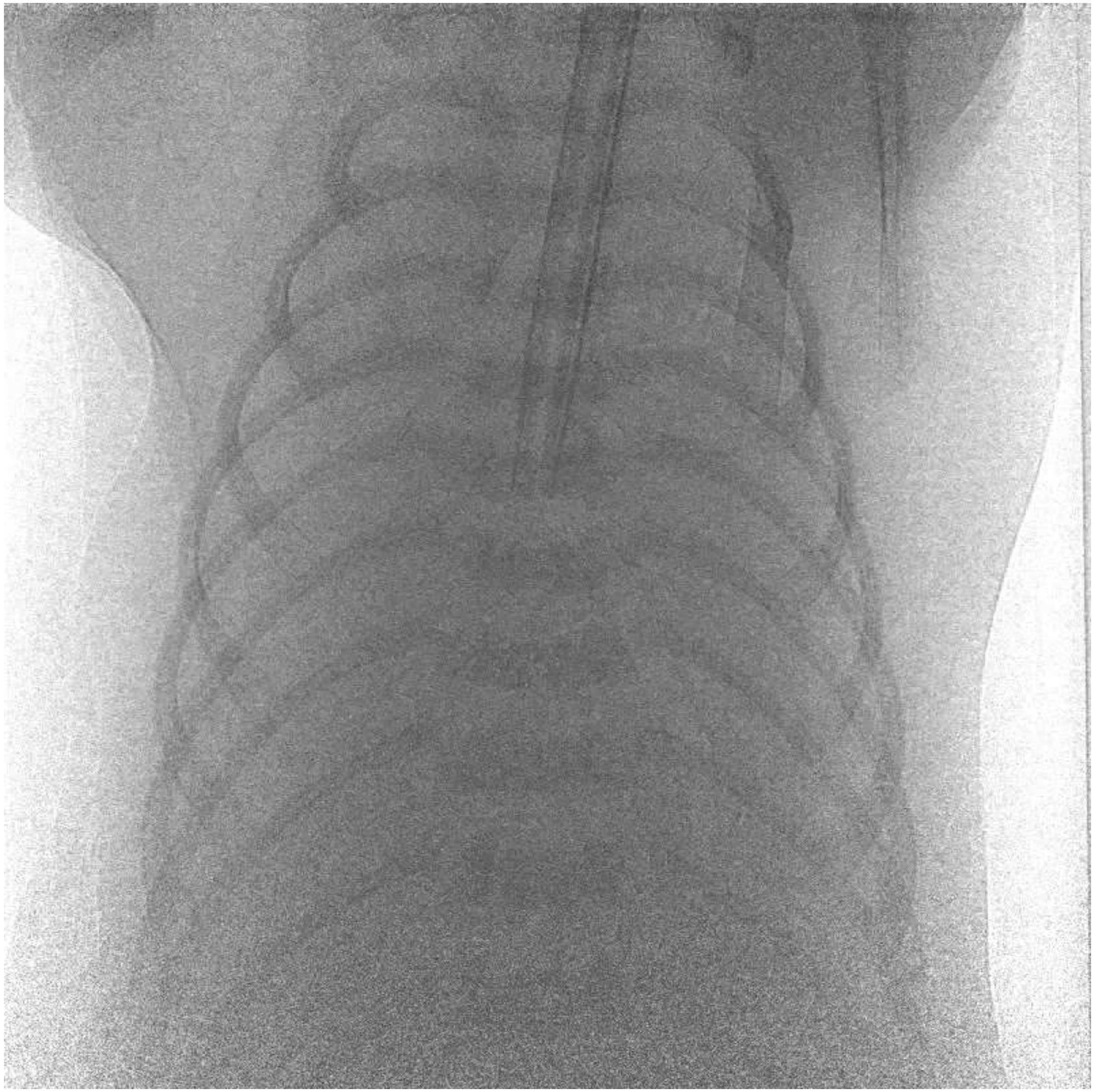


S Dubsky, A Fouras et al

4D Flow



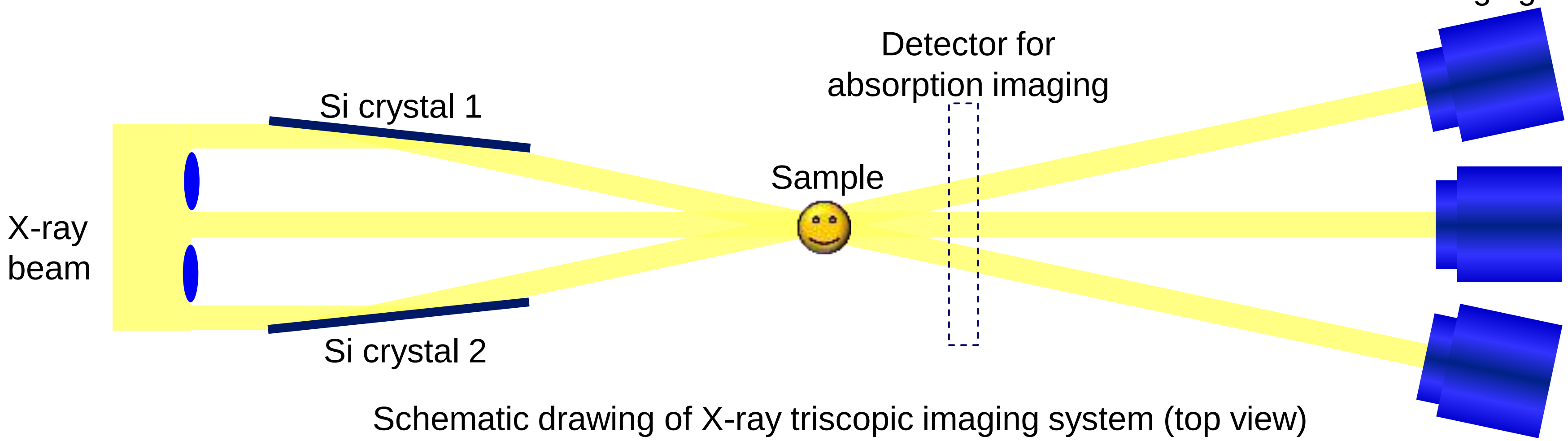
Simultaneous Phase Imaging and Angiography



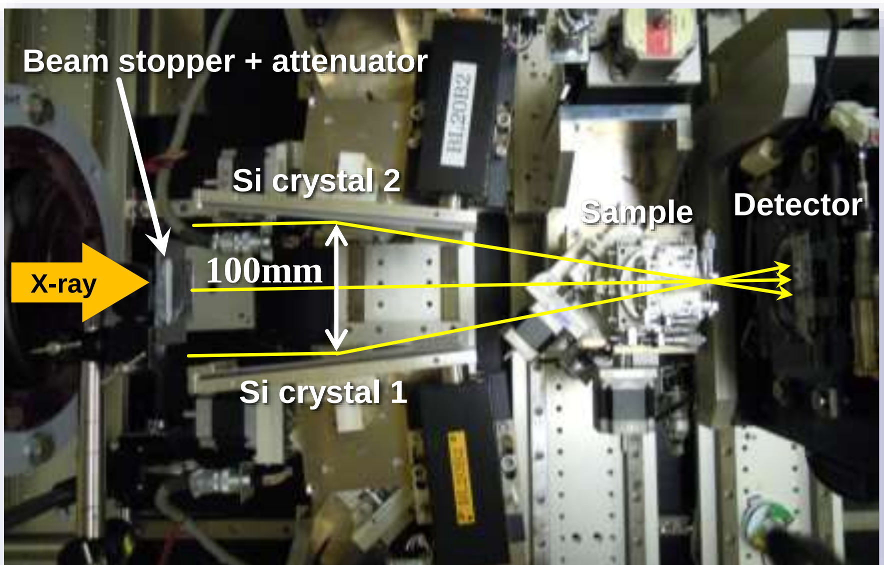
Major Problem: Technical

- Static beam greatly limits 4D imaging (x, y, z, t)

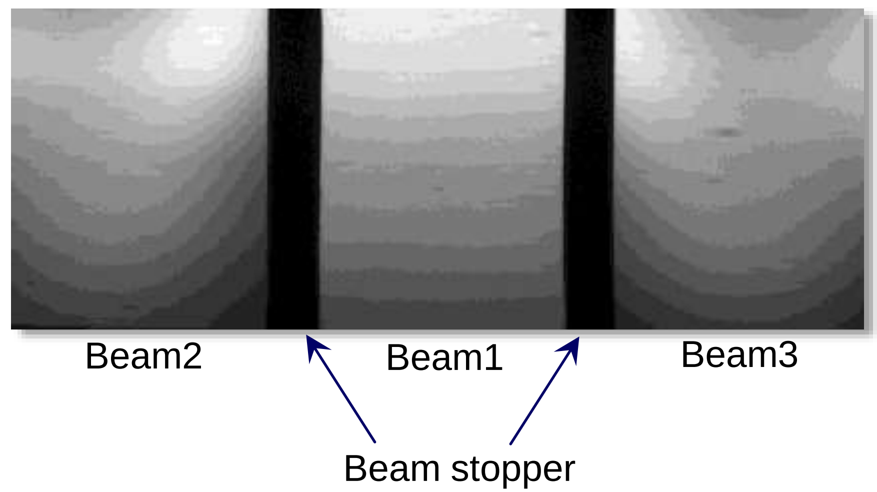
Setup for X-ray triscopic imaging



Schematic drawing of X-ray triscopic imaging system (top view)



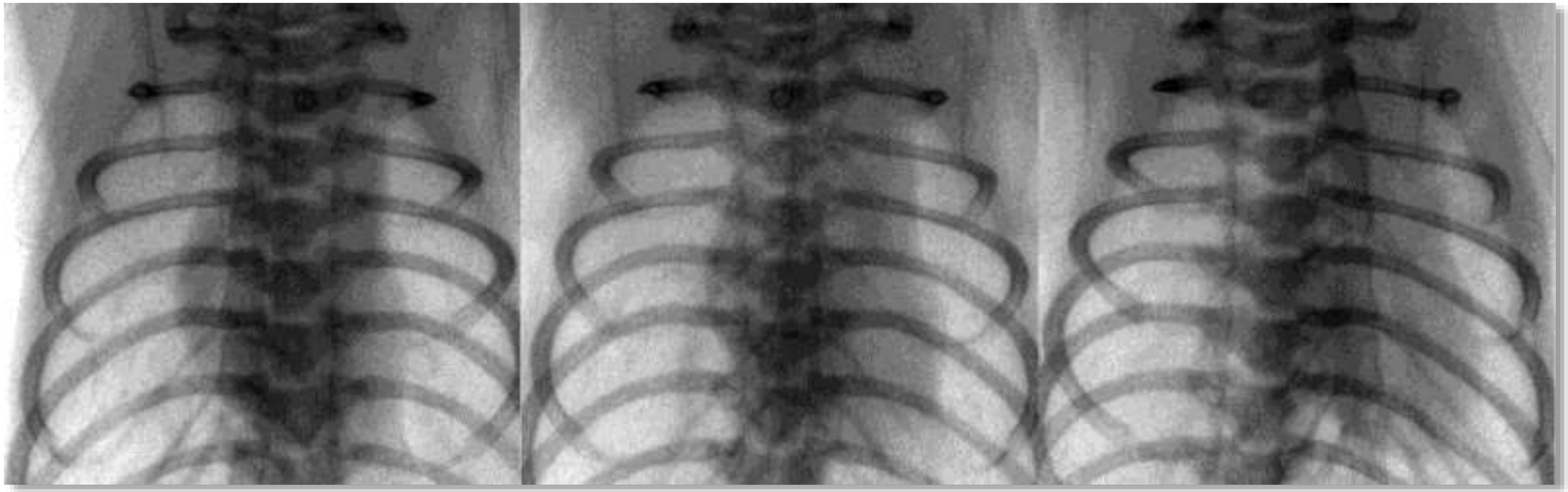
Picture taken from above of crystals and a sample



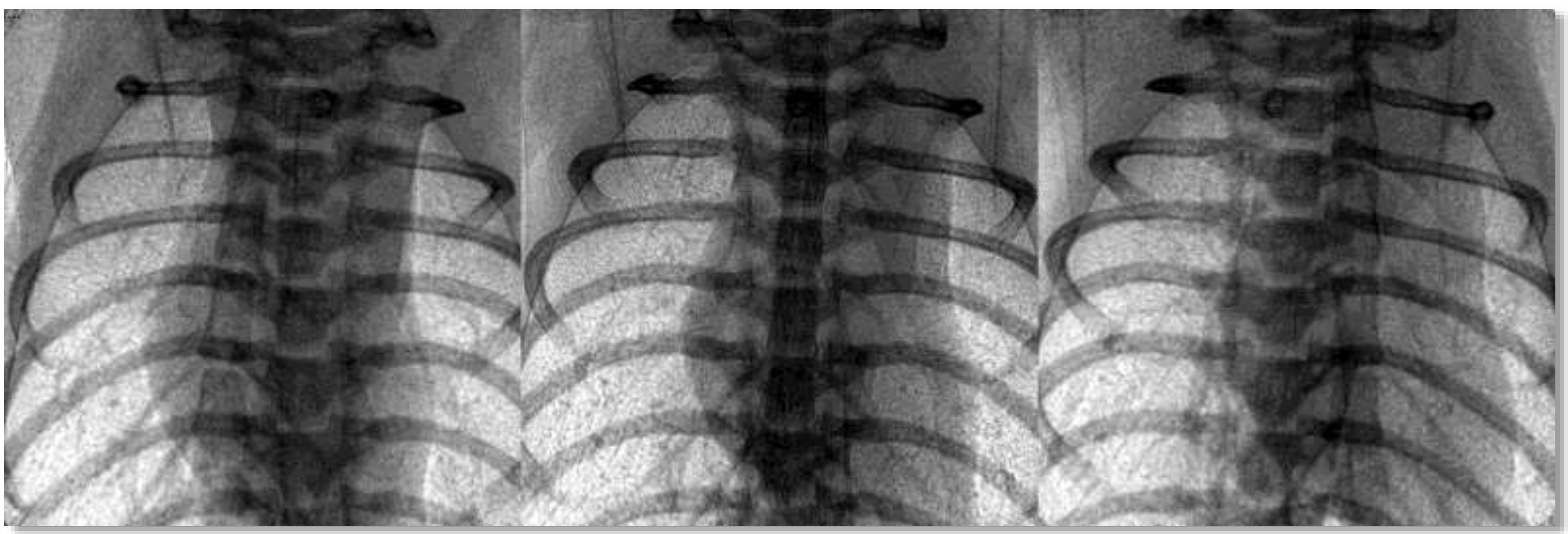
Raw three-beam image without sample

Masato Hoshino et al JSR Volume: **18** Pages: **569-574**

X-ray triscopic images of mouse chest



Absorption contrast image measured by single detector



Refraction contrast image measured by three detectors

Synchrotron Pros ‘n Cons

- Pros
  - Tunable Wavelength
    - Contrast specificity
    - Target elements
  - High Intensity
    - Short exposure times and hence movies
    - MRT
  - Scatter Reduction
    - Reduced dose, improved contrast
  - Phase Contrast
    - Reduced dose, improved contrast
- Cons
  - Fixed beam
    - Rapid CT very difficult
  - Limited availability
  - High Price

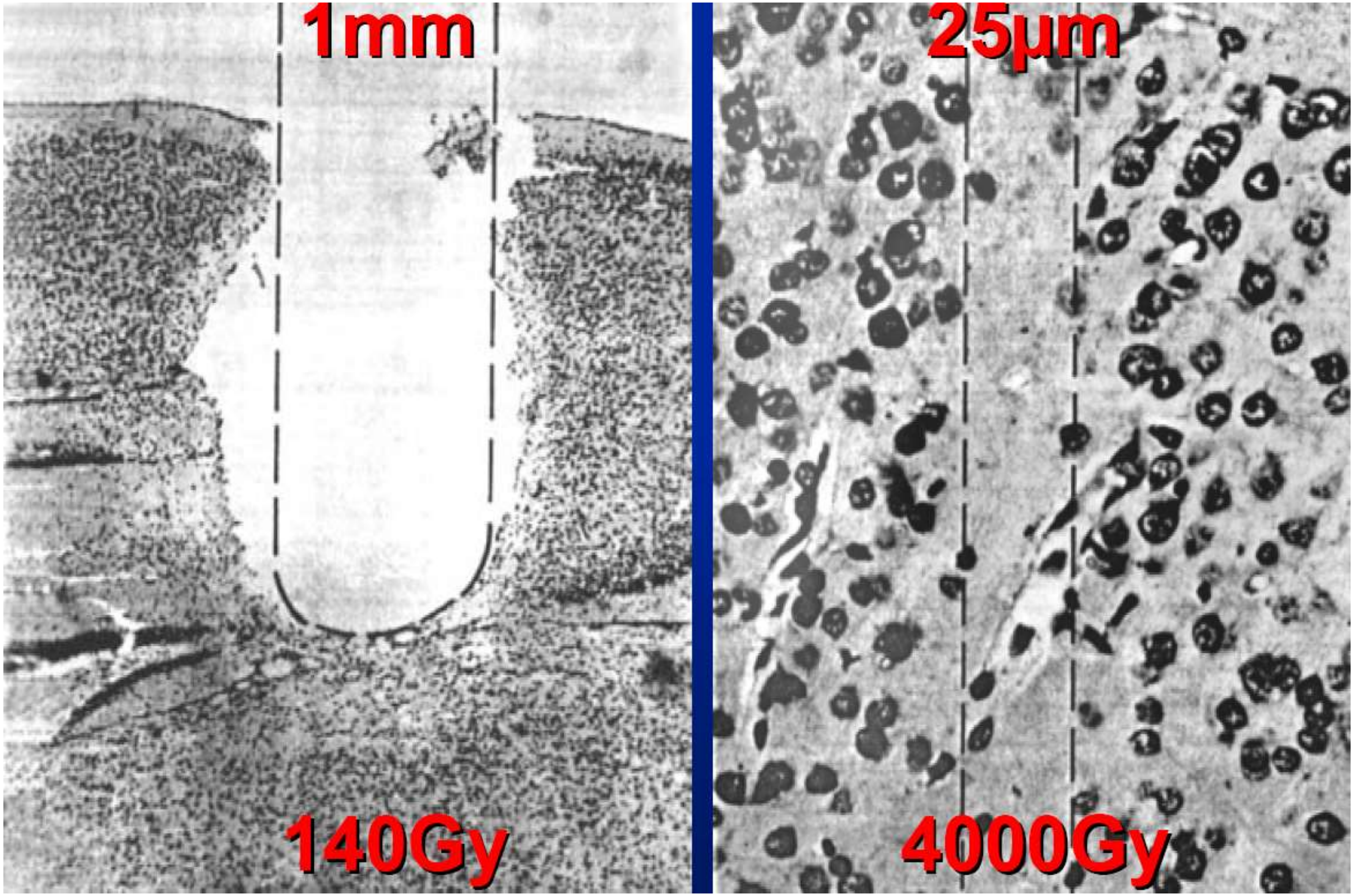
Radiotherapy

- The tumour can always be destroyed……
- …If we give it enough dose
- The question is…..
- ...Can we keep the patient alive and healthy whilst we do it?
- The radiation dose we can give to the tumour is limited by…..
- ..How much dose healthy tissue can tolerate whilst we try to zap the tumour

Radiotherapy

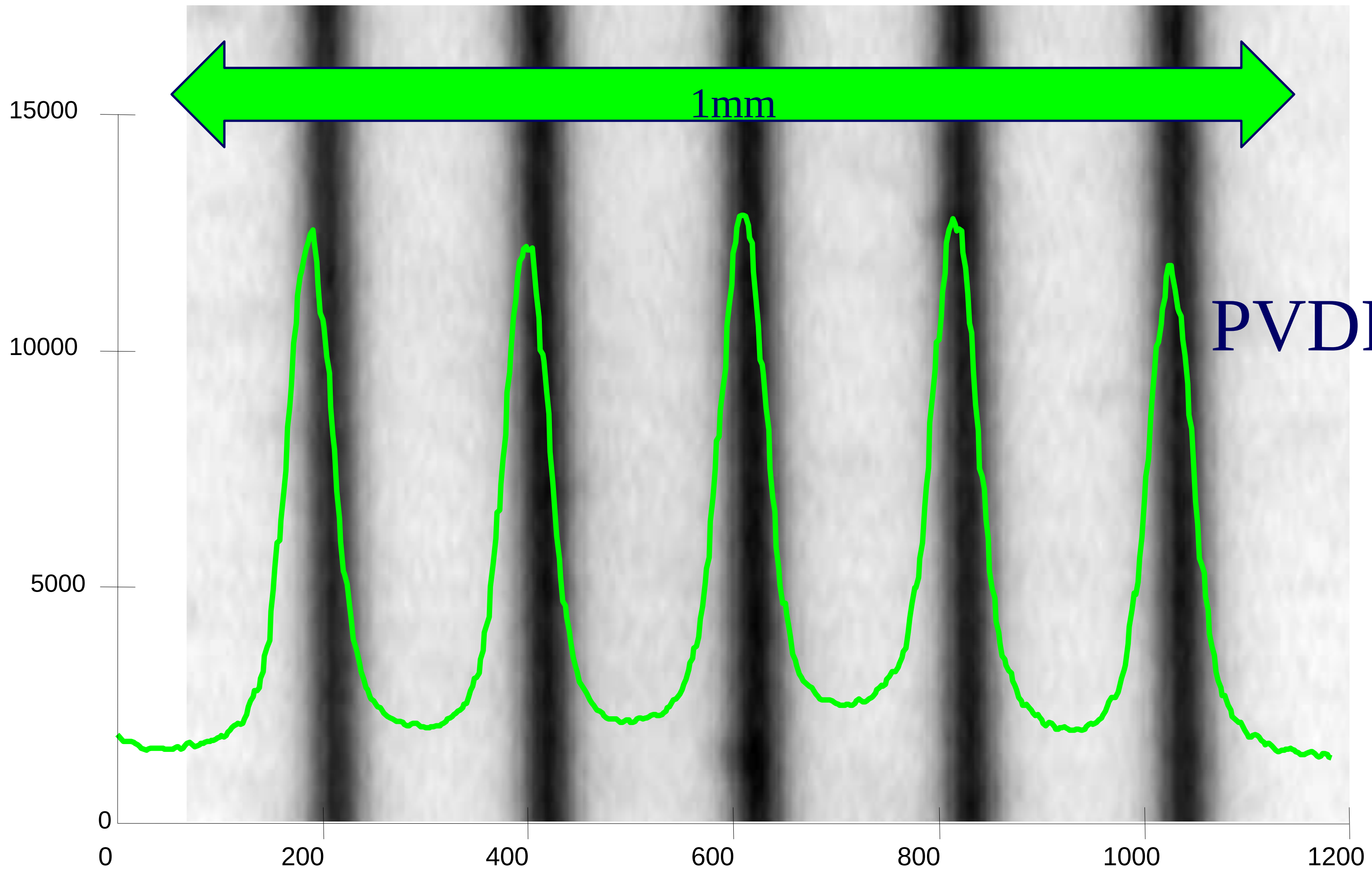
- The radiation dose that can be delivered to the tumour is limited by…..
- ..The tolerance of the surrounding healthy tissue
- Conventional Therapy
  - Uses a LINAC (high energy X-rays several MeV)
  - Uniformly irradiates tumour

Deuteron Beam: Mouse Visual Cortex



Zeman et al, Radiat Res 15 (1961) 496

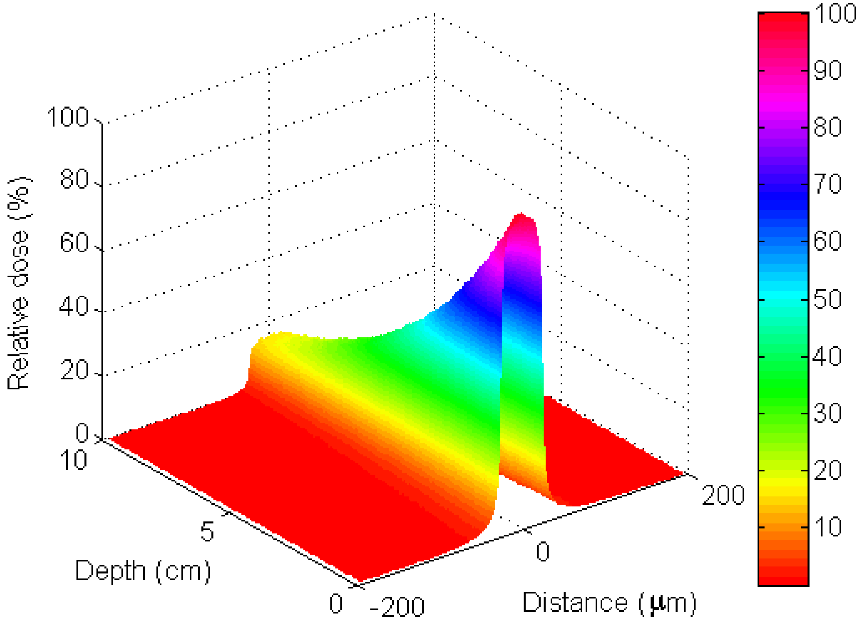
Peak to Valley Ratios



PVDR ~ 50

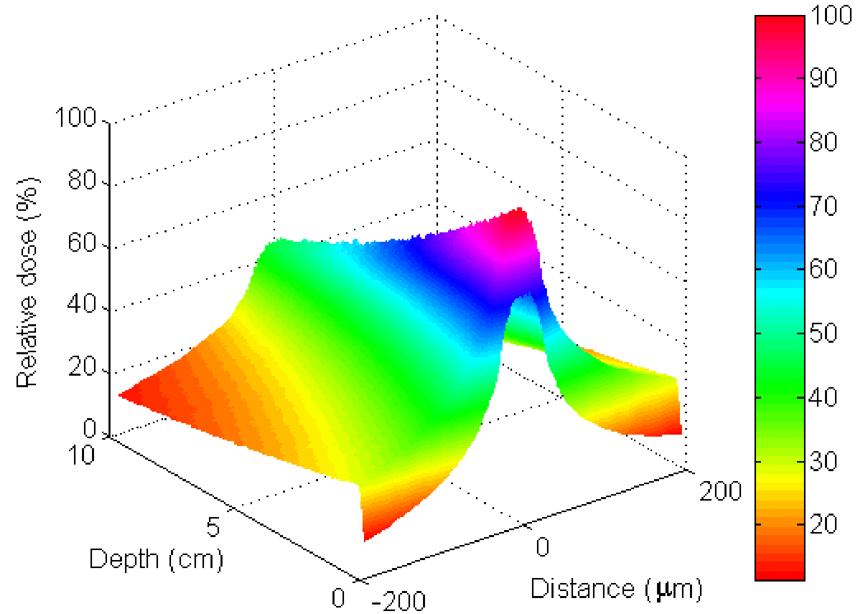
Position (μm)

Dose Depth Curves



Synchrotron Spectrum (~100keV)

1 MeV



Loss of Pattern with Depth

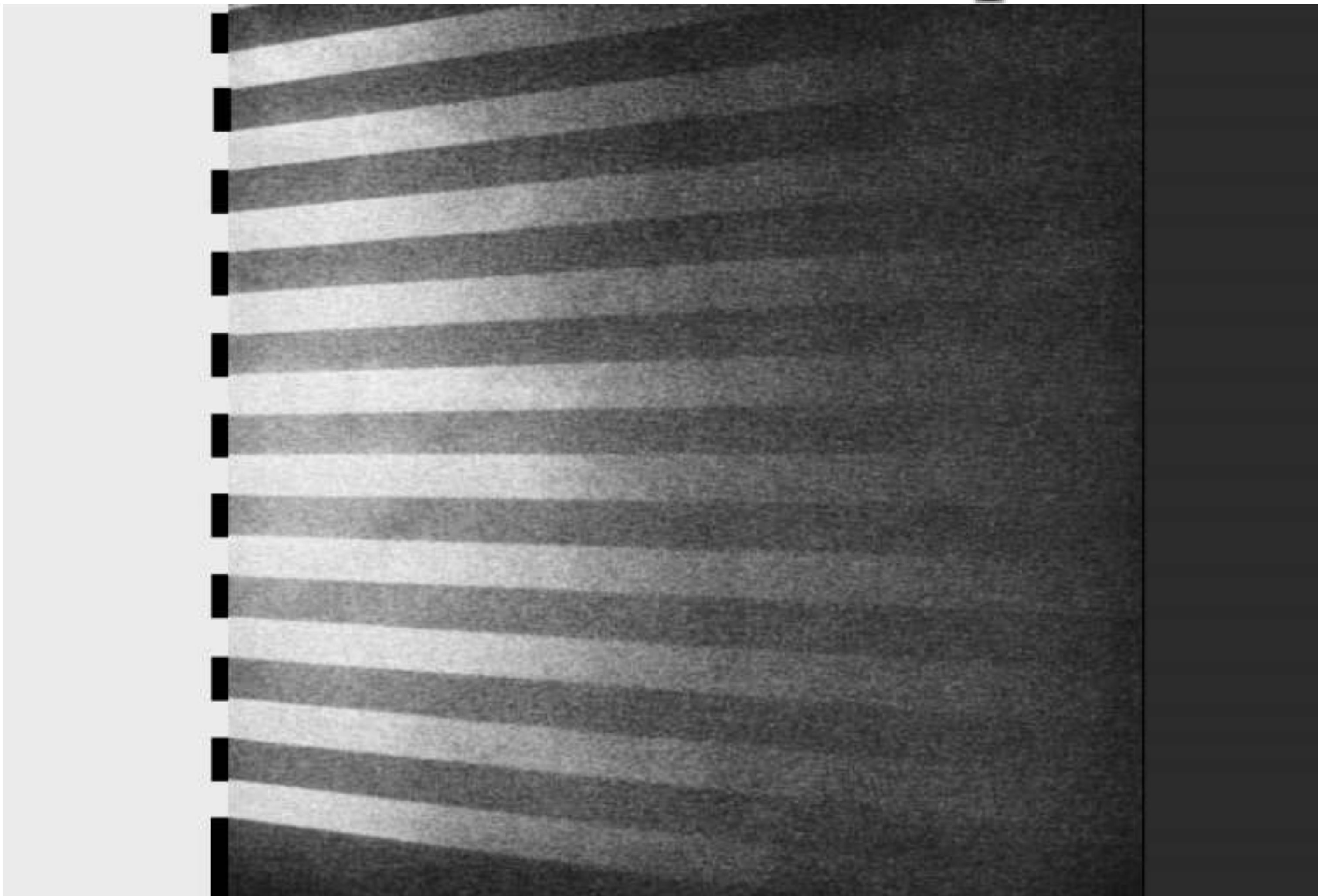
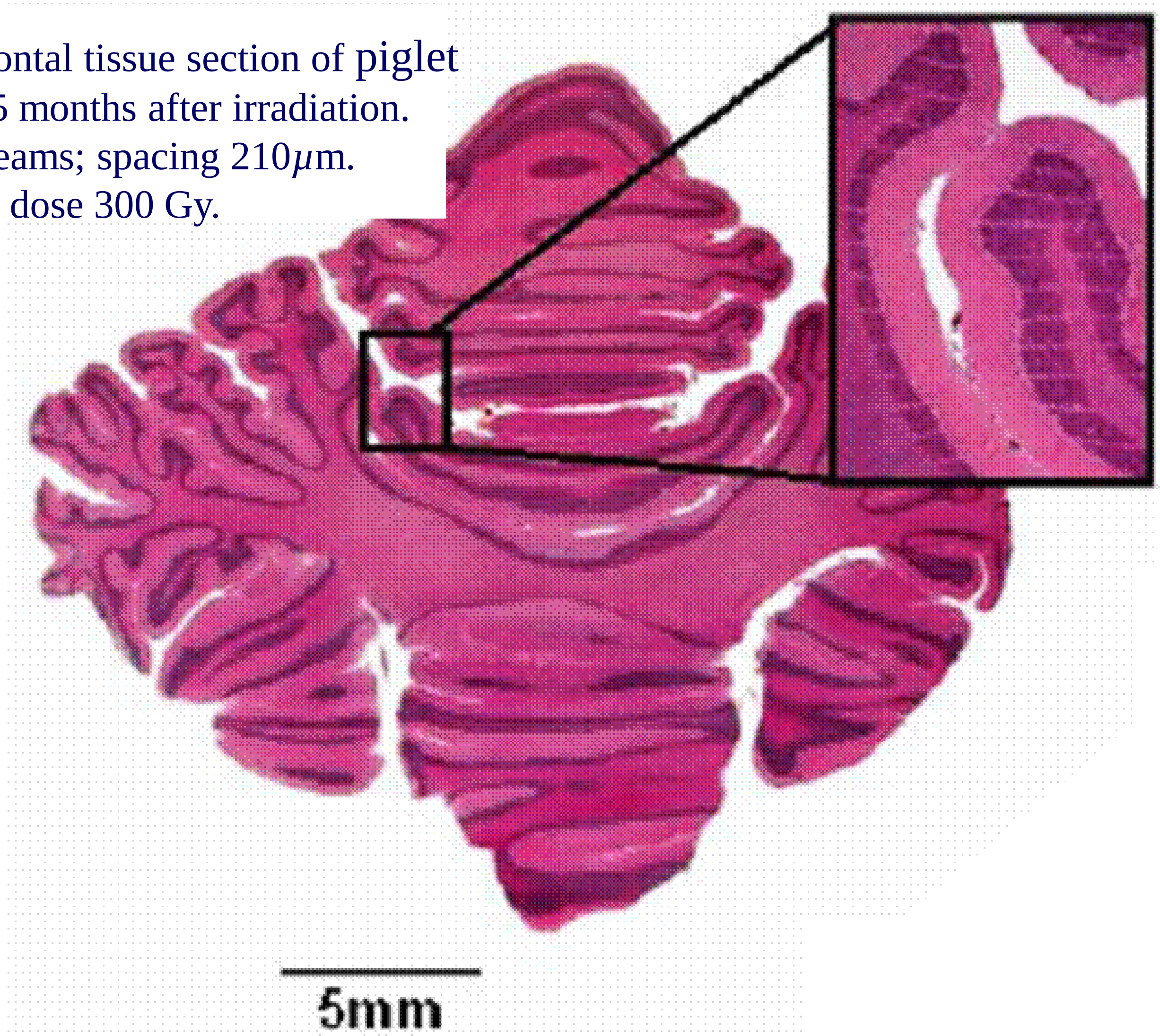


Fig. 43. Shafts of radiation through sieve fields showing divergence and obliteration of sieve pattern in depth

Jolles, 1953

Piglets

Stained horizontal tissue section of piglet cerebellum 15 months after irradiation.
25μm wide beams; spacing 210μm.
Skin entrance dose 300 Gy.

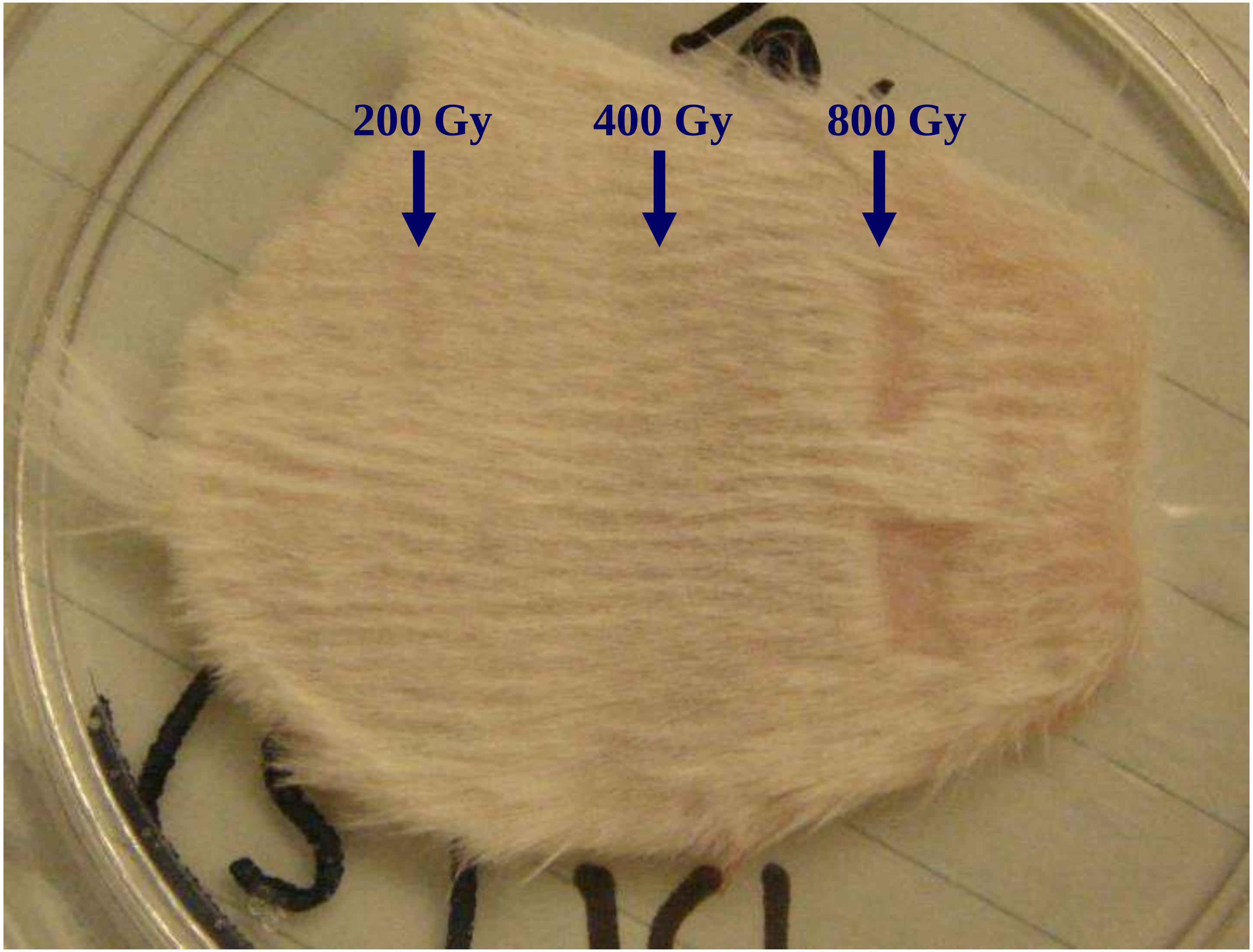


Laissue J A *et al* 2001 *Proc. SPIE* **4508** 65–73

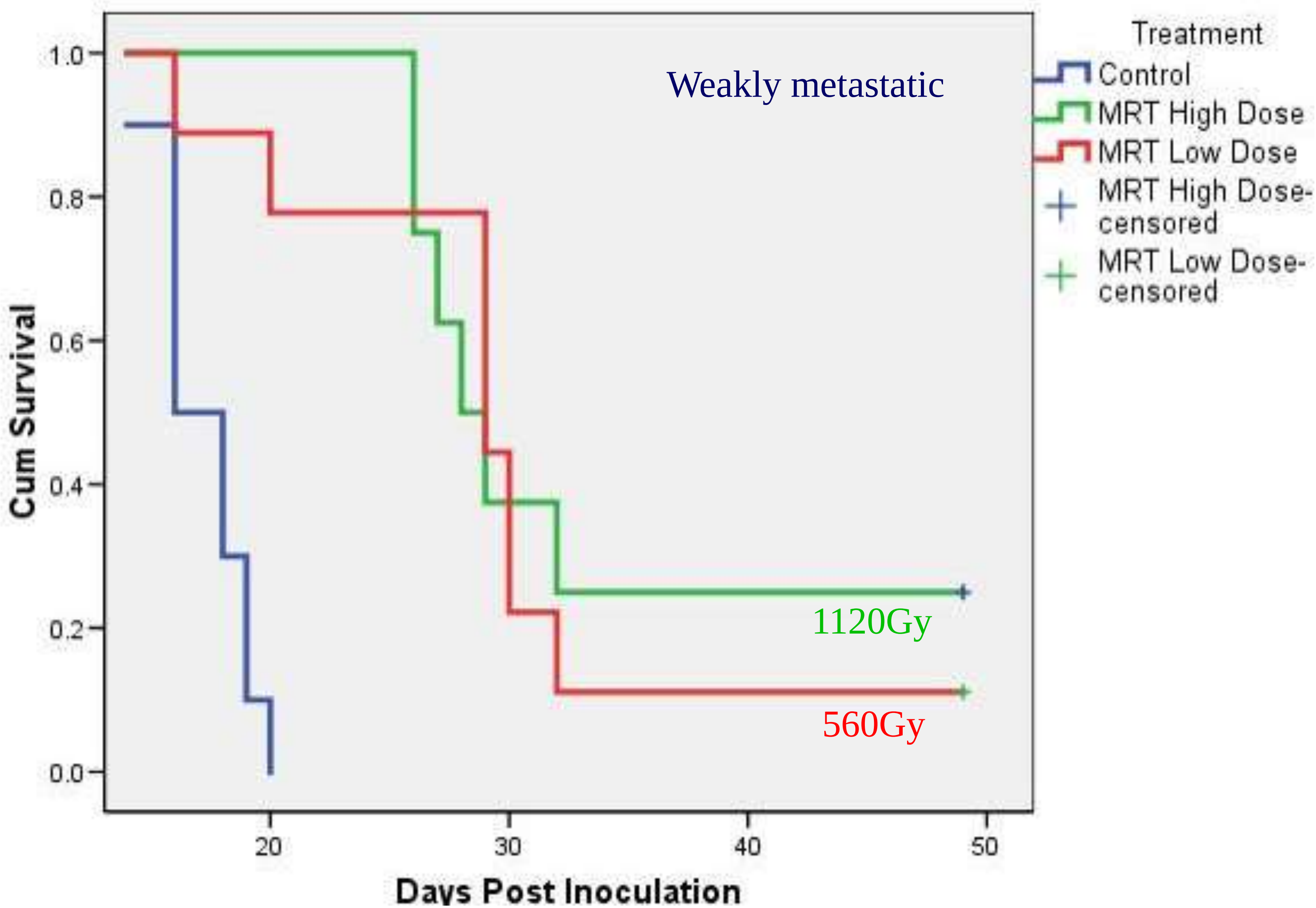
MRT on Mice

- Radiobiology of MRT is not well understood
- An understanding of the radiobiology is crucial for the optimisation of MRT and for any clinical implementation
- Understanding MRT will also inform conventional radiotherapy
- Mice are by far the best characterised mammal
  - Many GM mouse models already available
  - Many assays have been developed

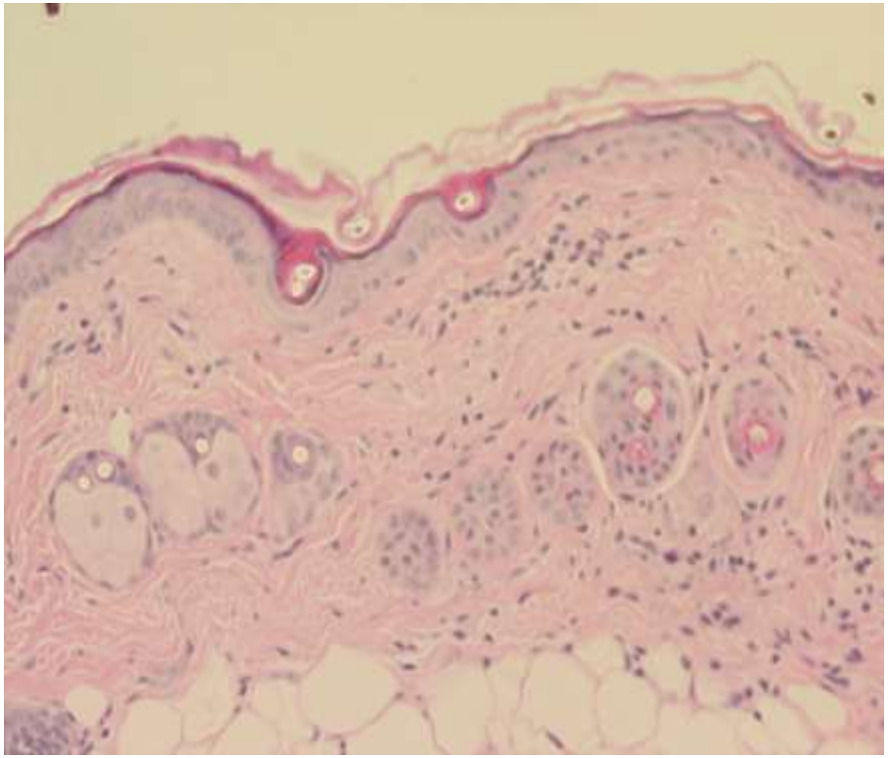
Exfoliation

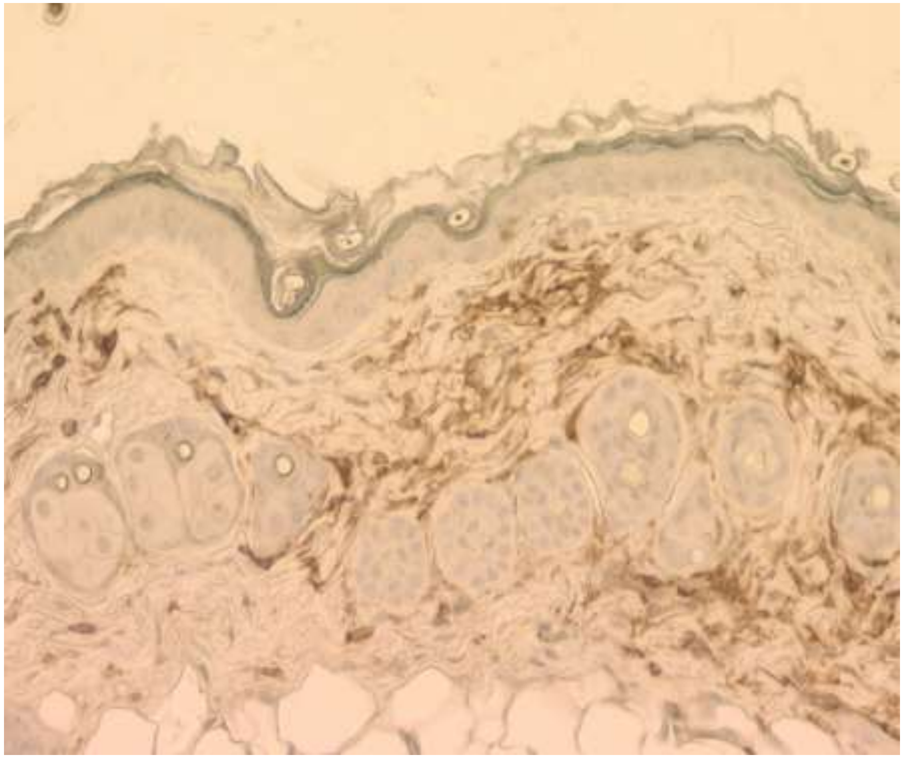


Survival Fractions EMT 6.5



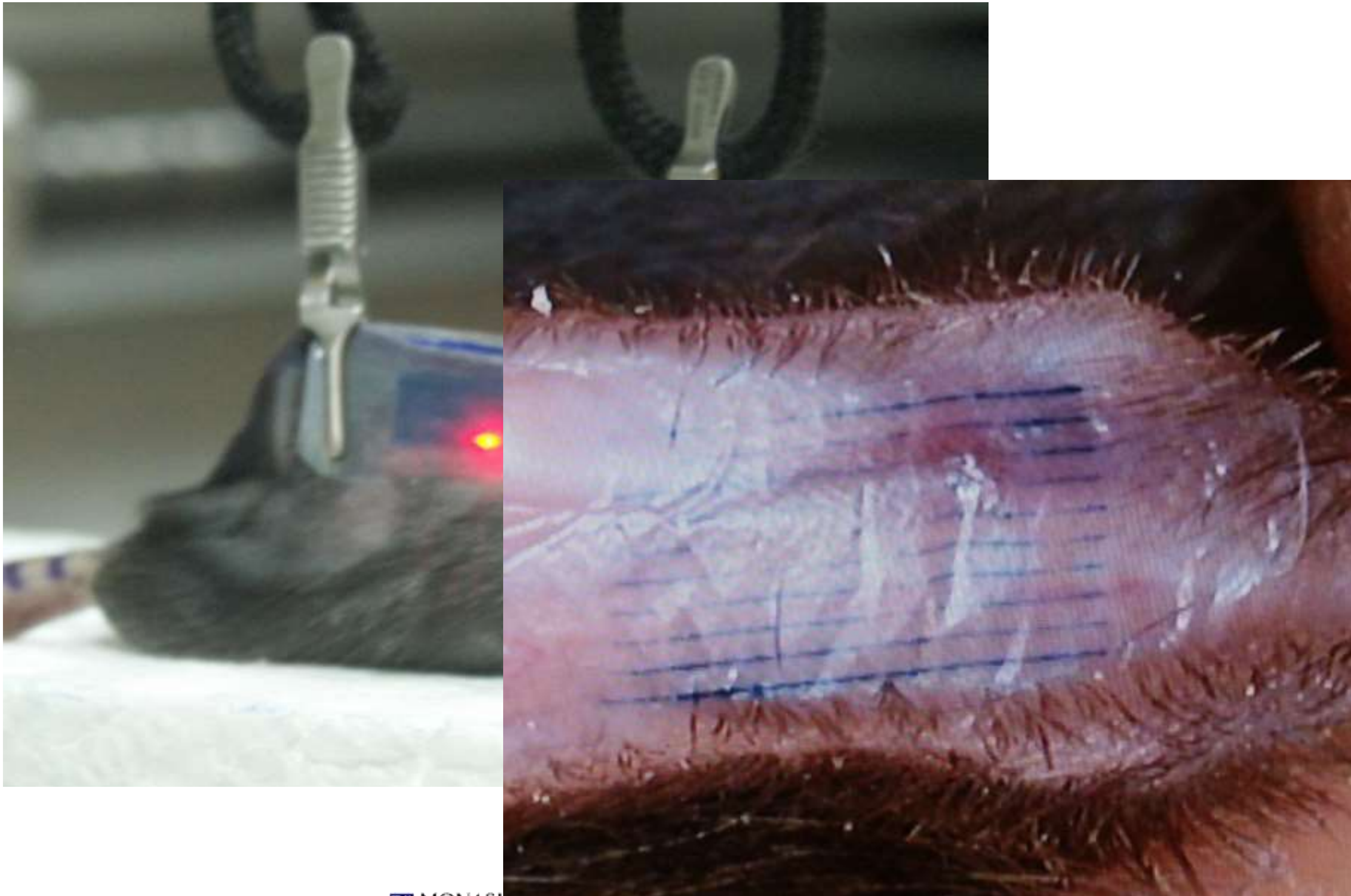
Results - Immunohistochemistry





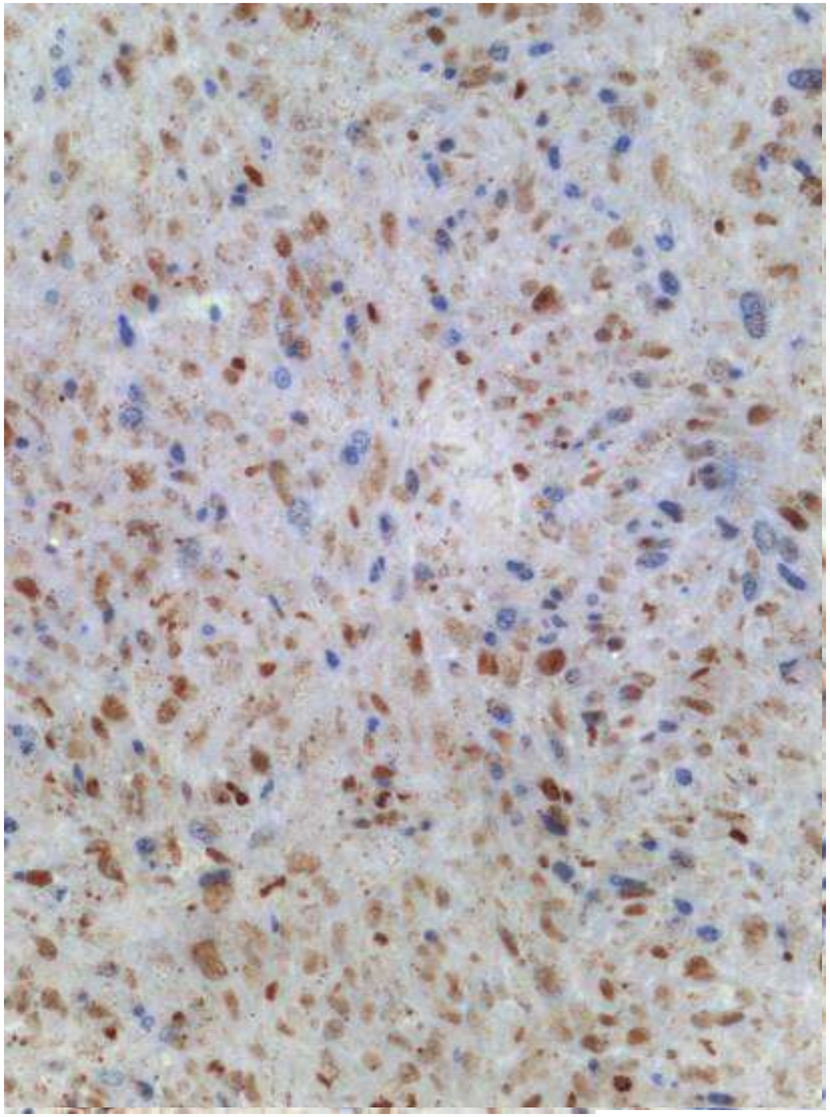
- H&E and CD45 Leukocyte Common Antigen (LCA) Staining of MRT-irradiated Mouse skin 5.5 days PI   (x 100)
- Intact hair follicles & sebaceous glands

Using Radiochromic Film to Locate Microbeams

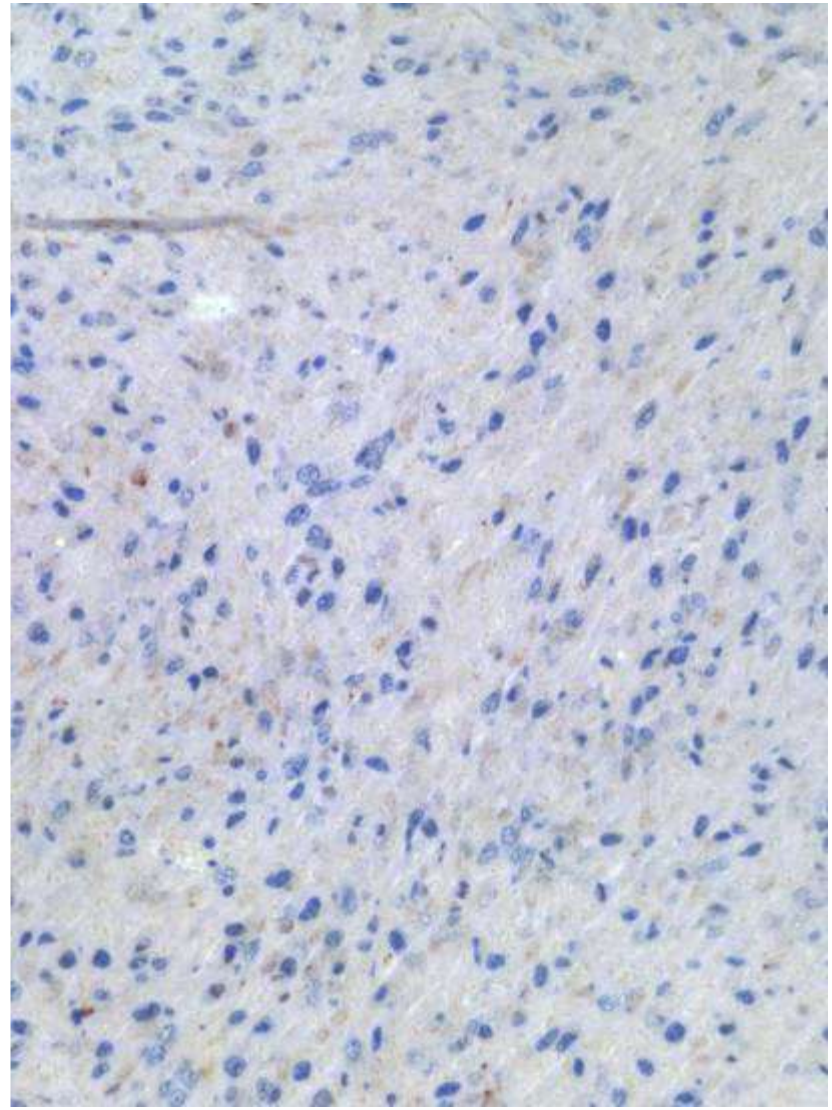


γH2AX/BrdU IHC post 560 Gy

MRT treated



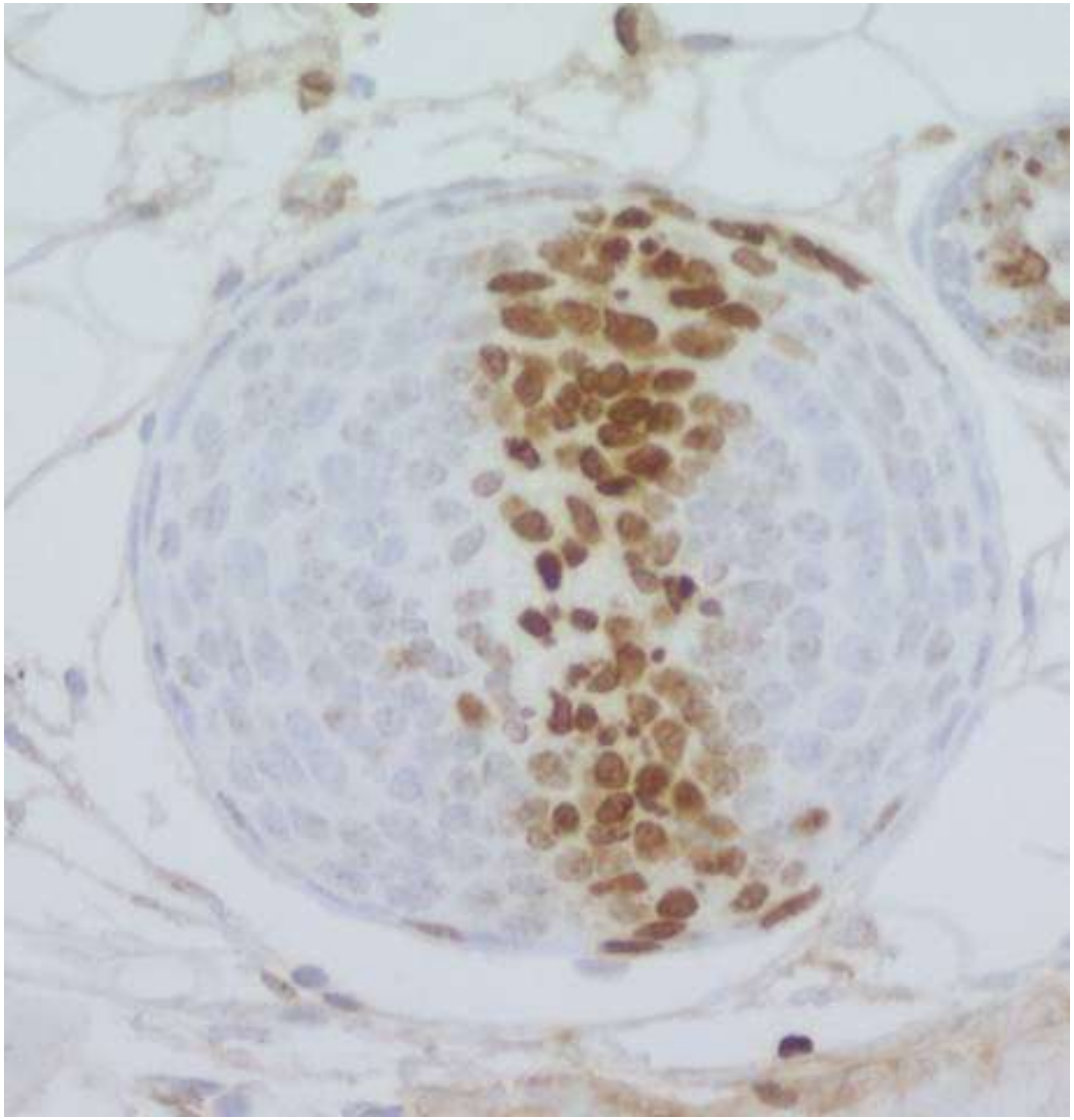
Control



48 hours after irradiation

University of Saskatchewan MONASH University Jeff Crosbie, Peter Rogers, Robyn Anderson, Rob Lewis

Splitting Hairs!



Conclusions

- X-rays are here for a while
- Synchrotrons have an important role in developing new x-ray methods in medicine
- In order to translate the research into the clinic, some human studies are necessary
- Much can be achieved with animal studies

The Team

- Stuart Hooper
- Megan Wallace
- Marcus Kitchen
- Melissa Siew
- Beth Allison
- Andreas Fouras
- Karen Siu
- Arjan te Pas
- Chris Hall
- Naoto Yagi
- Kentaro Uesugi
- Kaye Morgan
- Sally Irvine
- David Parsons
- Peter Rogers
- Jeff Crosbie