Imaging and Radiotherapy with Synchrotron X-rays

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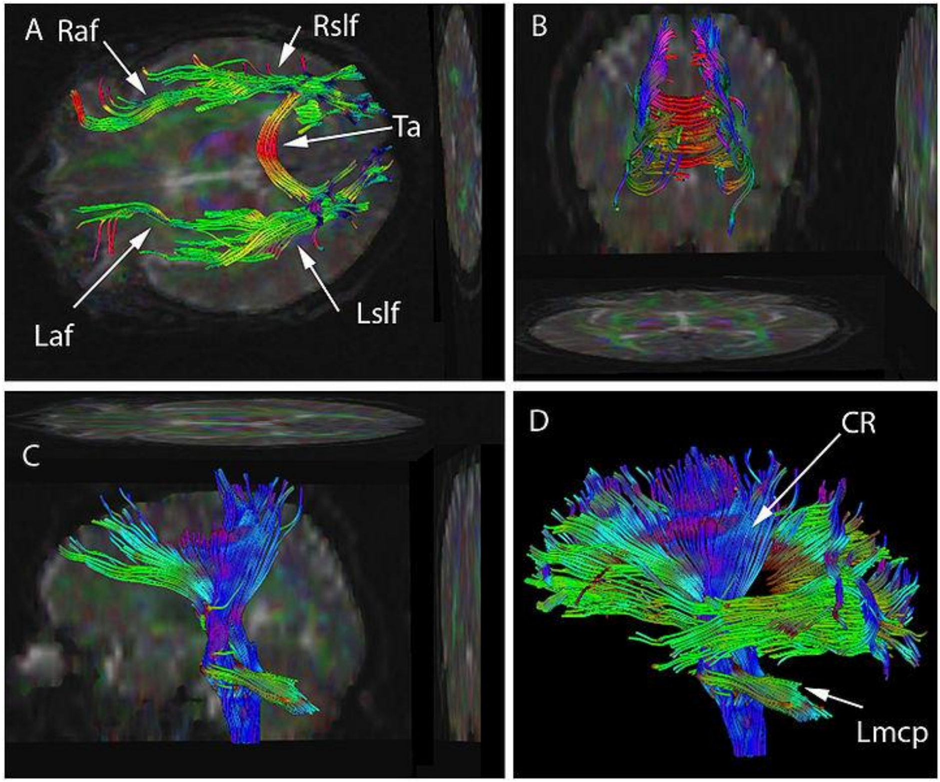
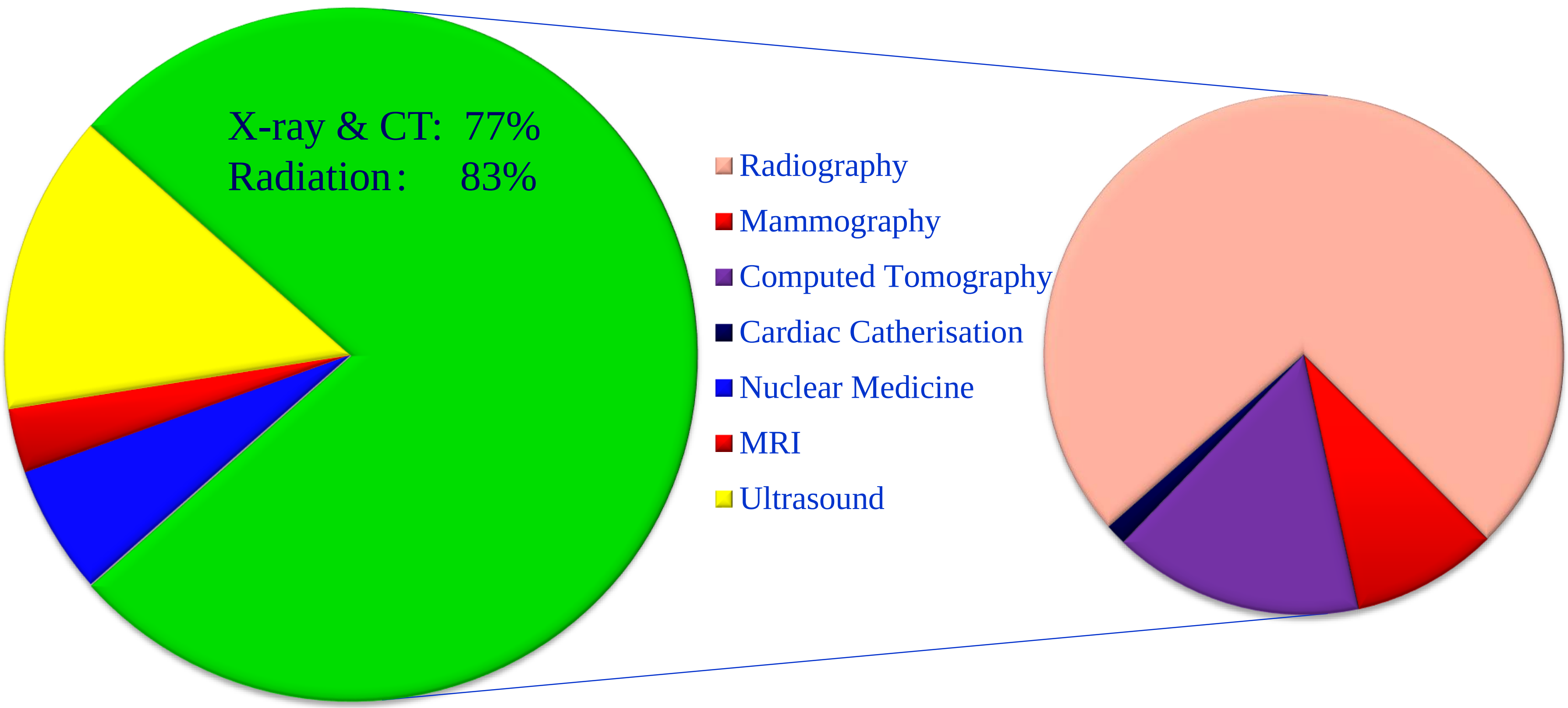
Other Modalities

- 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 Canada



Source: Canadian MIS Database, Candian Institute for Health Information 2007 with thanks to Paul Babyn

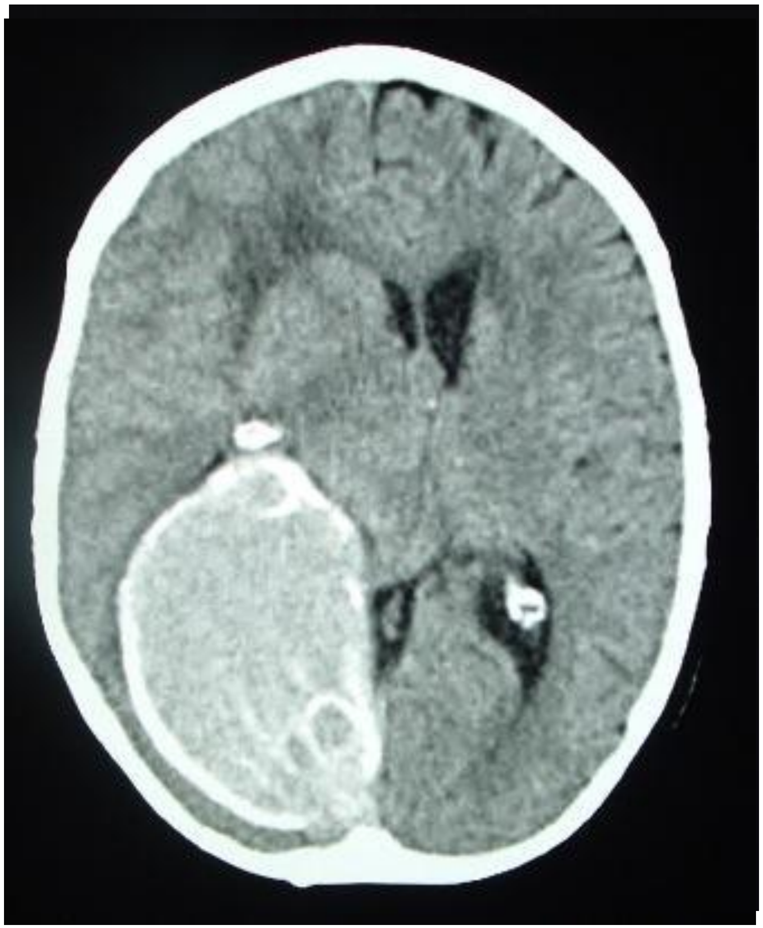
MRI

- Cost:
  - **CT:** From $700 to $2,200
  - **MRI:** From $1200 to $4000
- Time taken for complete scan
  - **CT:** Usually completed within 5 minutes
  - **MRI:** Typically 30-40 minutes

MRI Accidents

MRI-CT Comparison

CT



MRI

http://www.ct-scan-info.com/head-ct.html

MRI-CT Comparison

CT

MRI

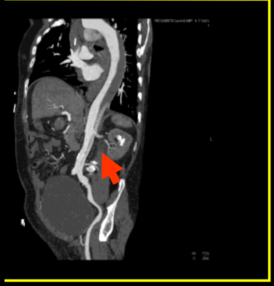
http://www.ct-scan-info.com/head-ct.html

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



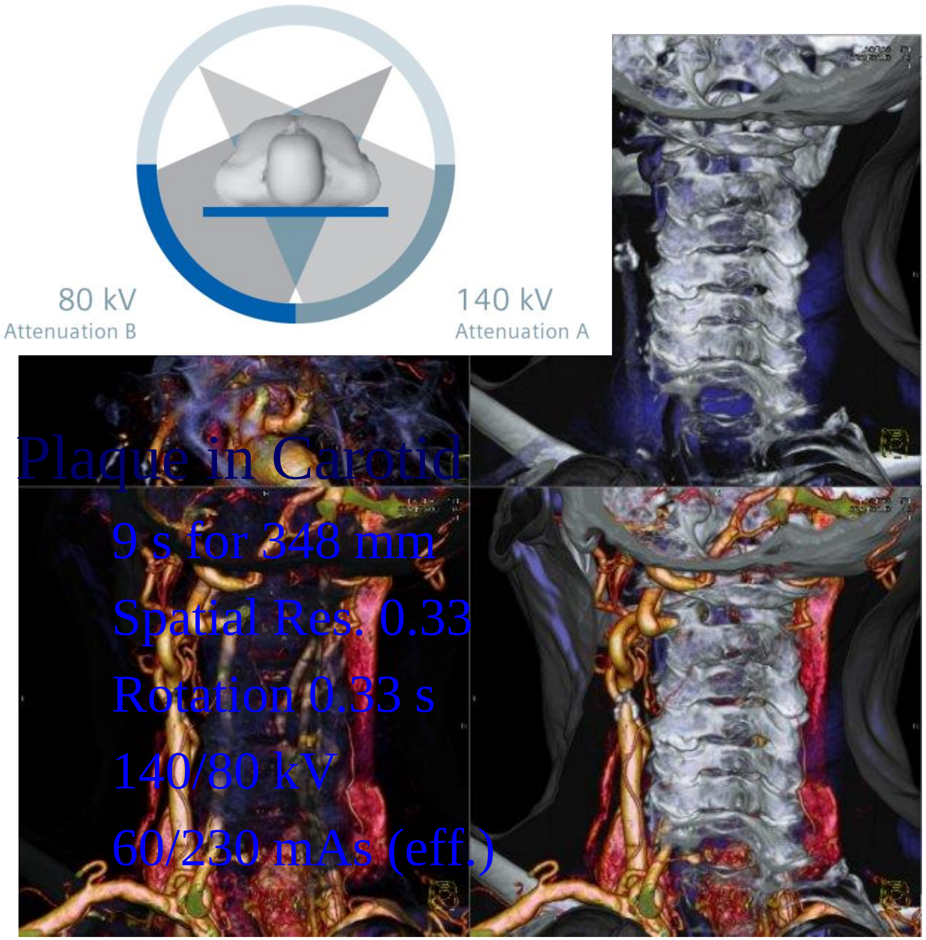
SOMATOM Definition Flash

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

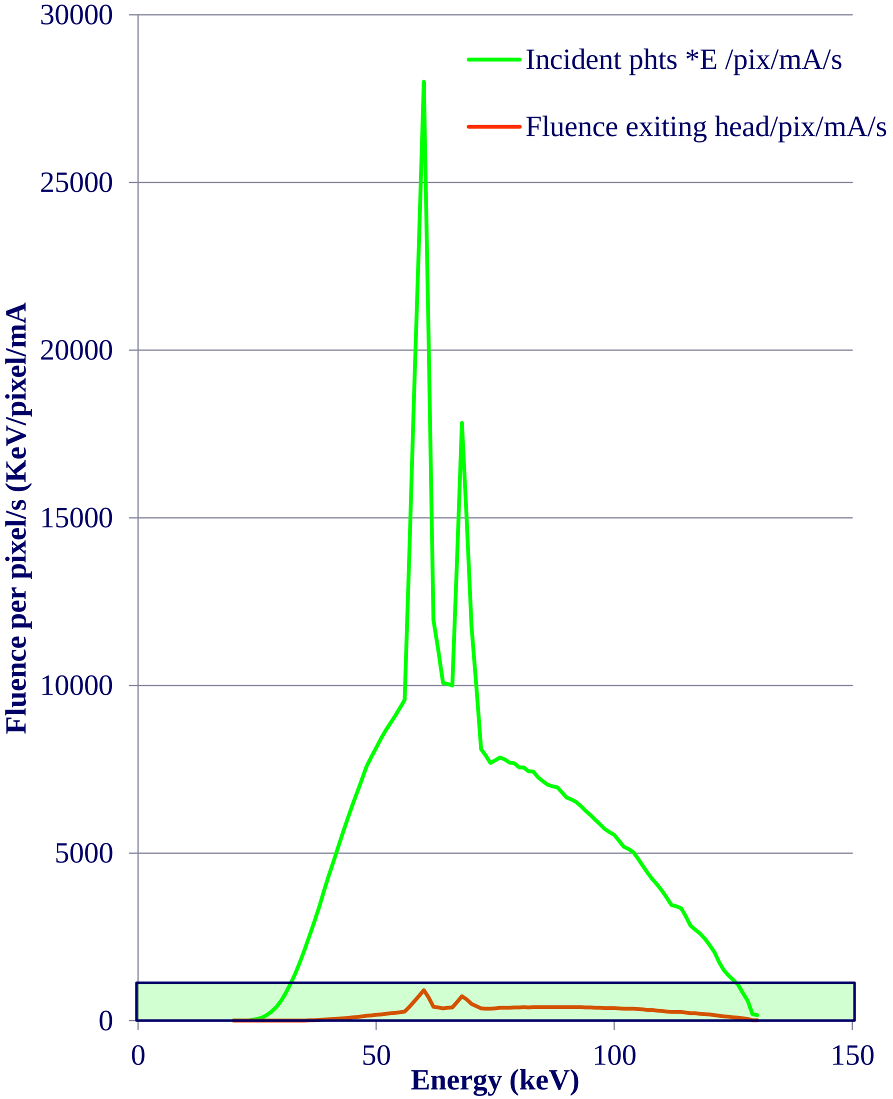
Dual Energy CT

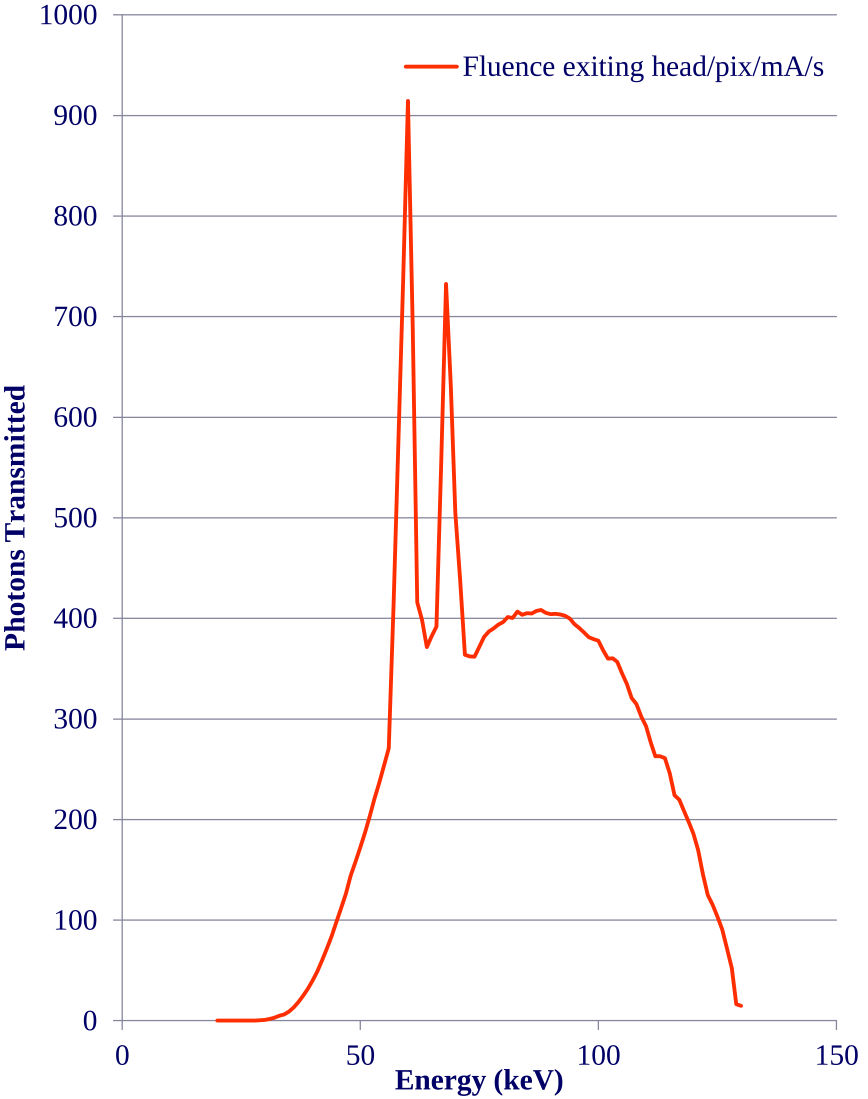


Plaque in Carotid

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

Fluence and Dose

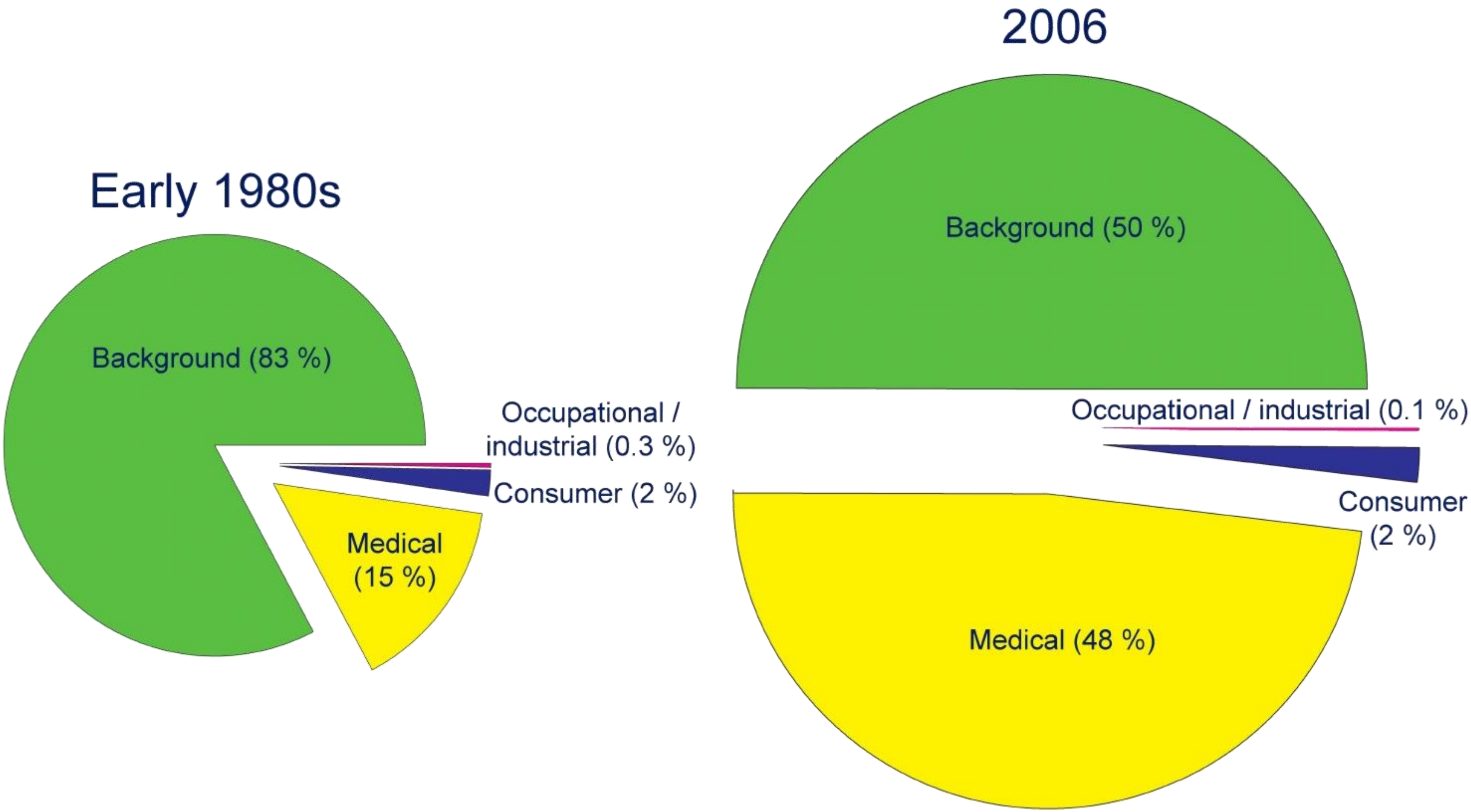




What is the Risk from Radiation?

- 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
- On 31 May, Fukushima prefecture dose rate was 1.5μSv/h
  - 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

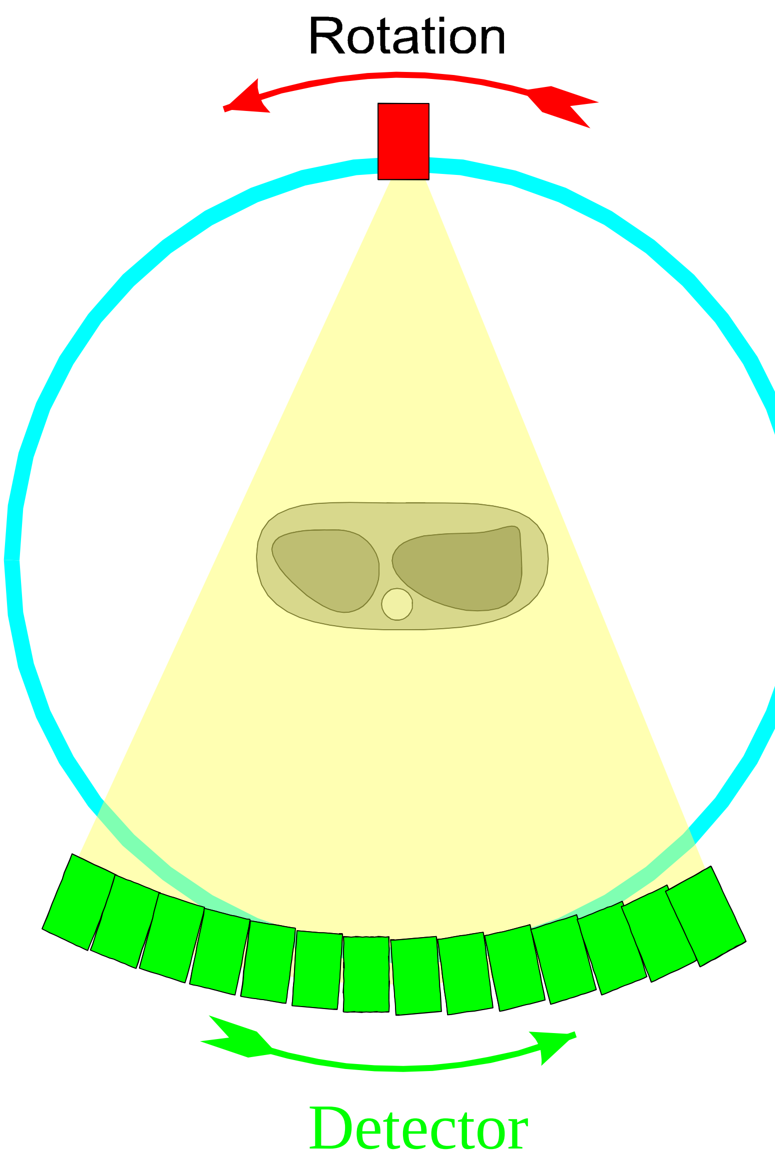
Trends in Radiation Dose from Medical Imaging



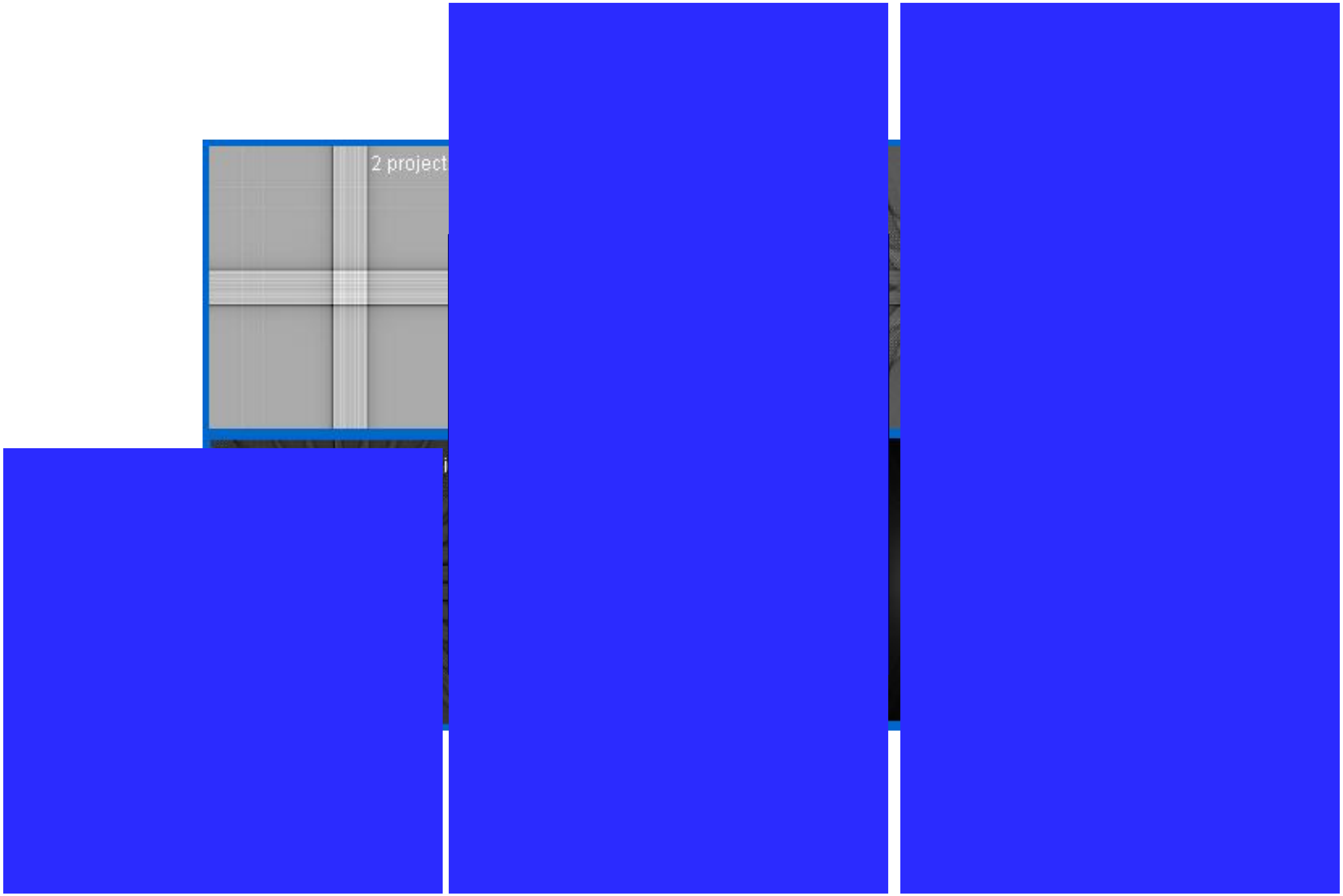
	Early 1980s	2006
Collective effective dose (person-Sv)	835,000	1,870,000
Effective dose per individual in the U.S. population (mSv)	3.6	6.2

3rd Generation CT Scanner

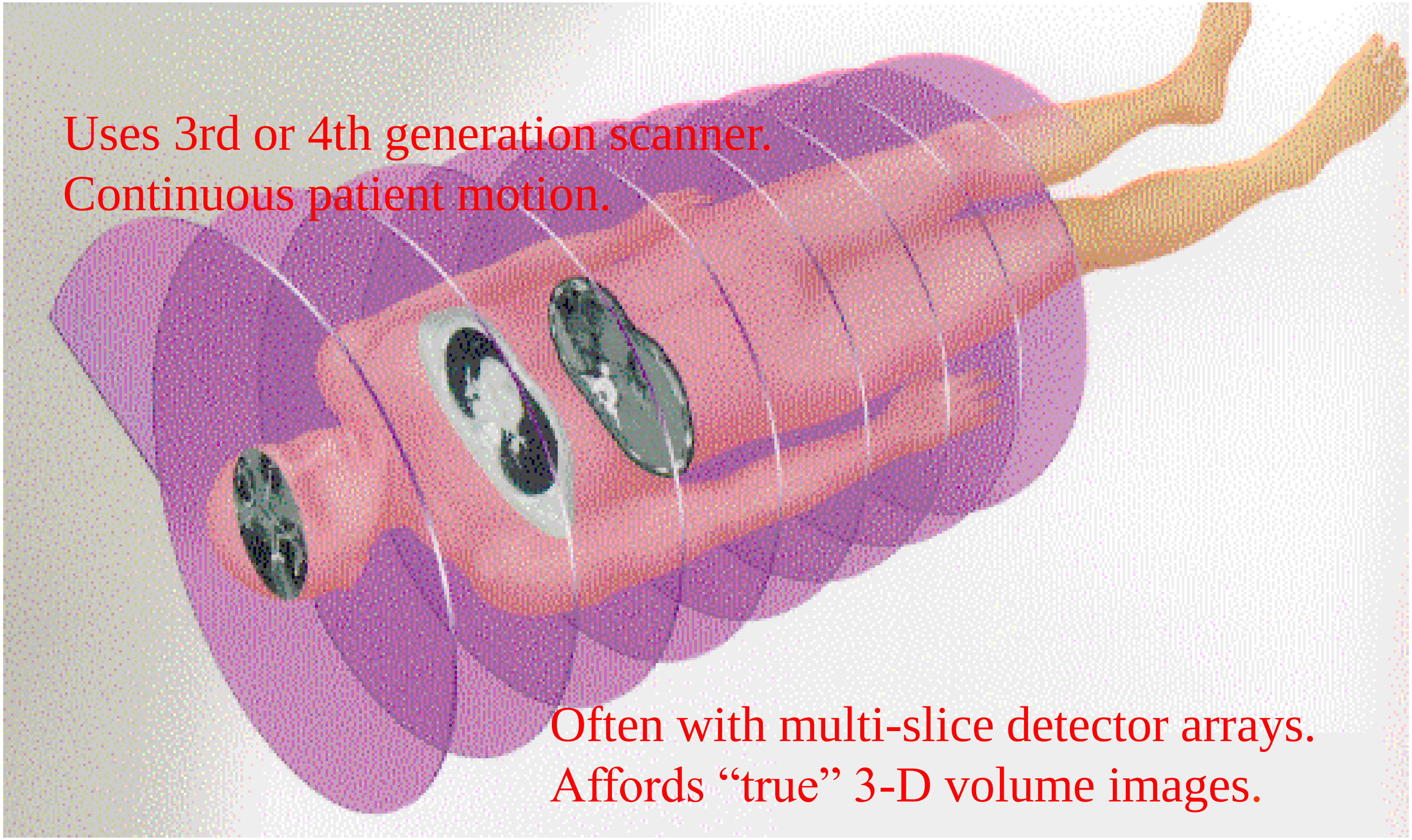
- Multiple detectors
- Translation-rotation
- Large fan beam
- Patient stationary for each 2-D slice acquisition; about 0.1 seconds per slice
- kV = 120, mA = 500
- Image then reconstructed in about 0.1 seconds



FBP in Practice



Volume CT image



Beam Harding Artefacts

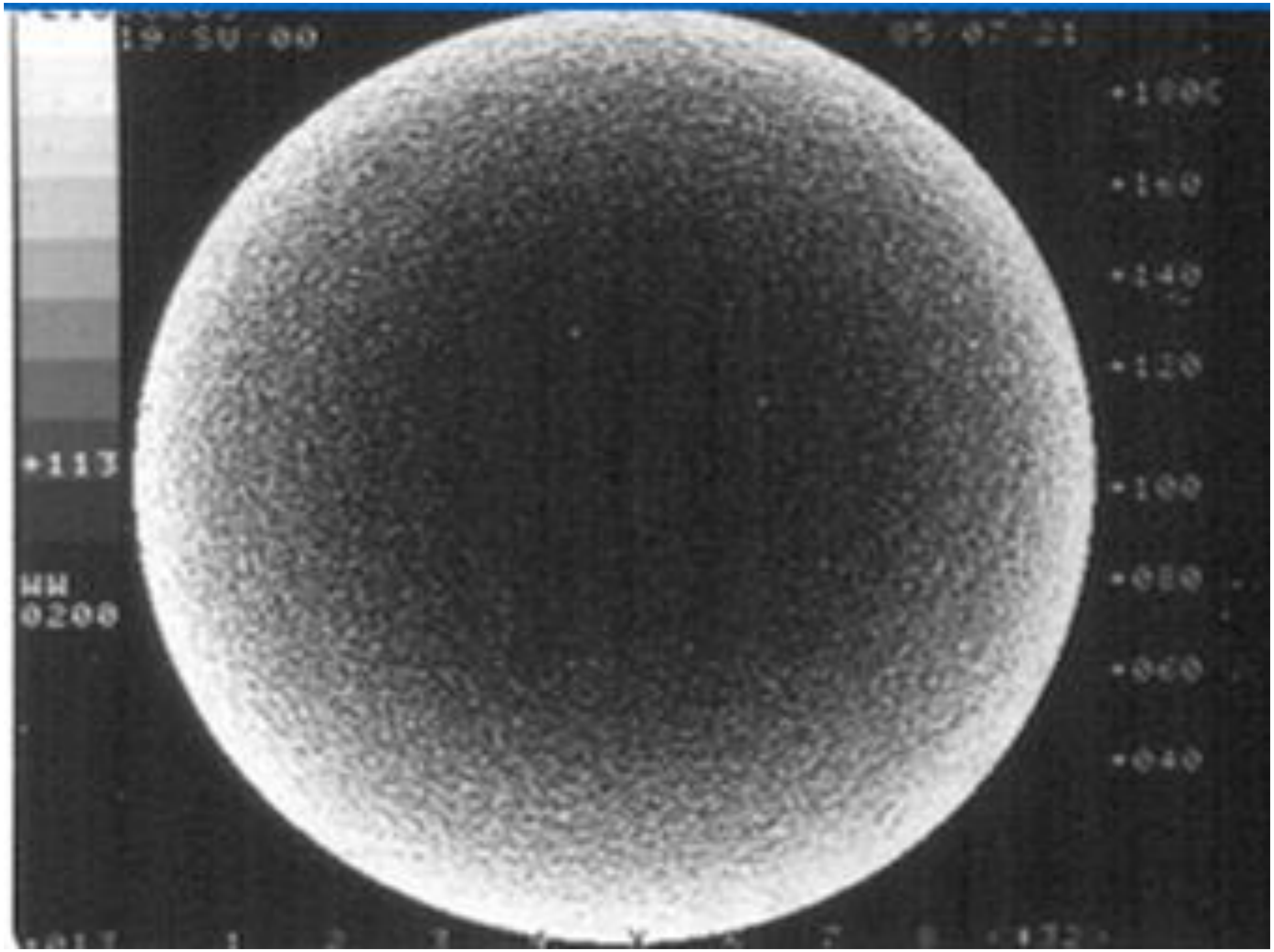
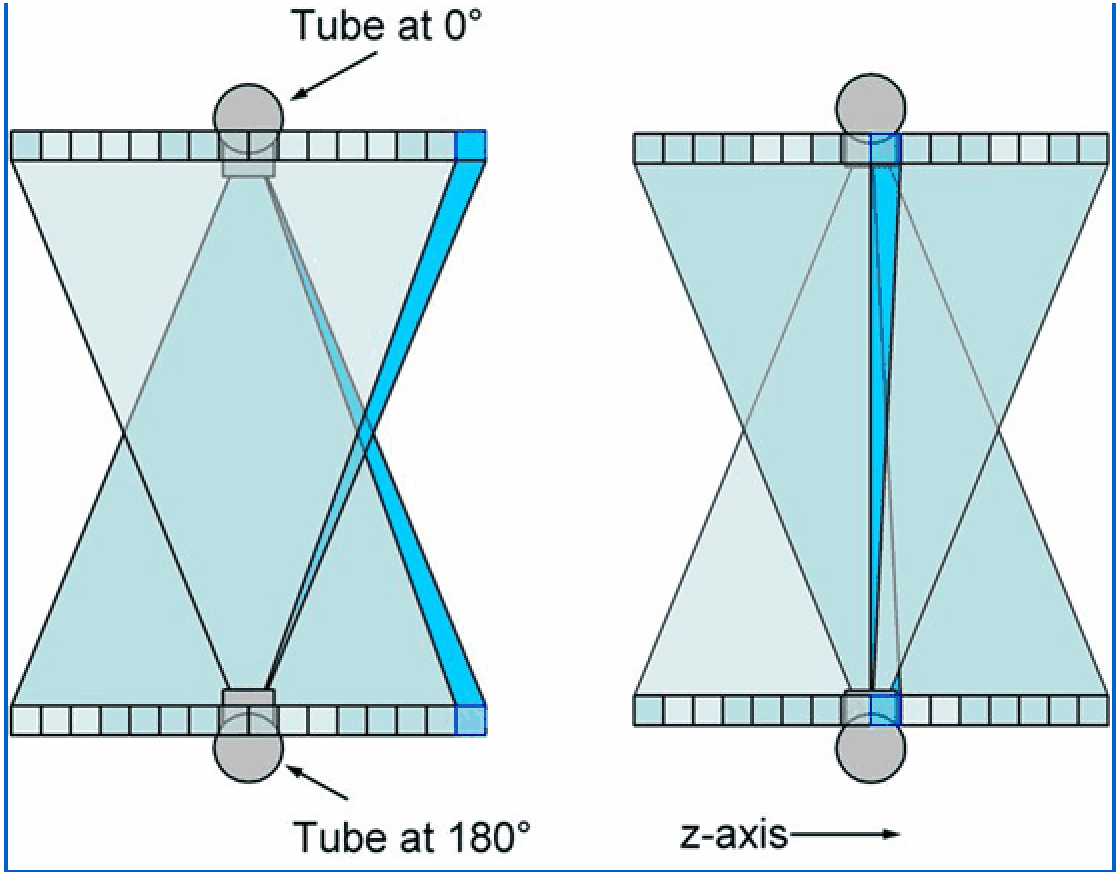
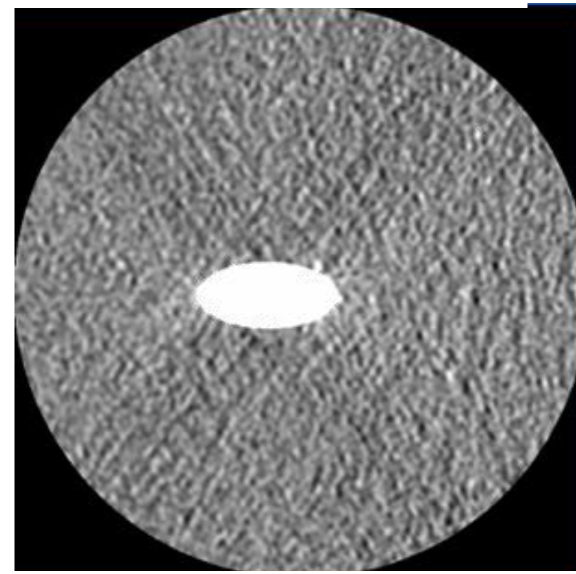


Image of uniform phantom

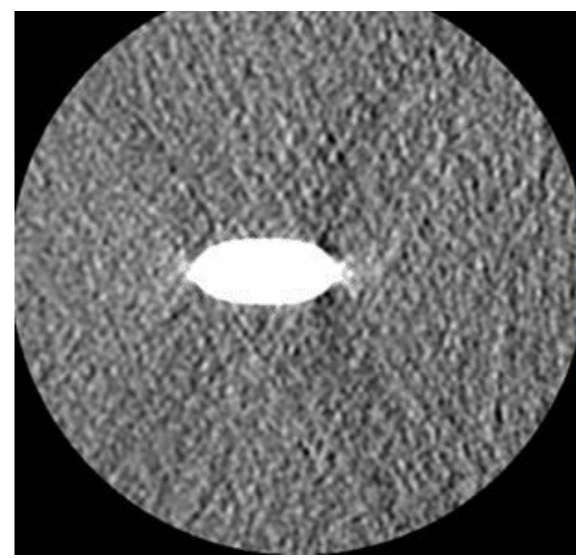
Cone Beam Artefacts



Inner detector row image



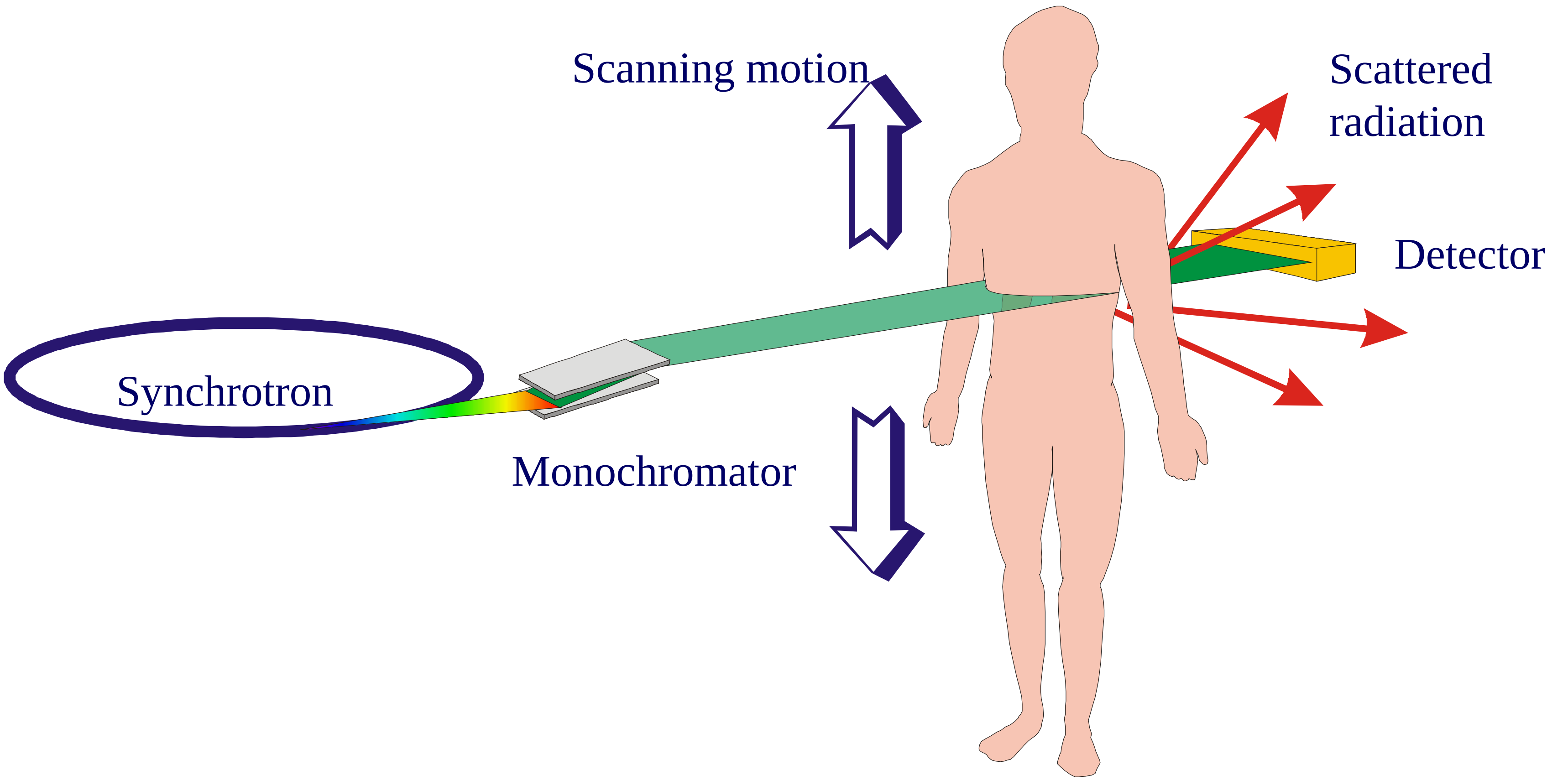
Outer detector row image



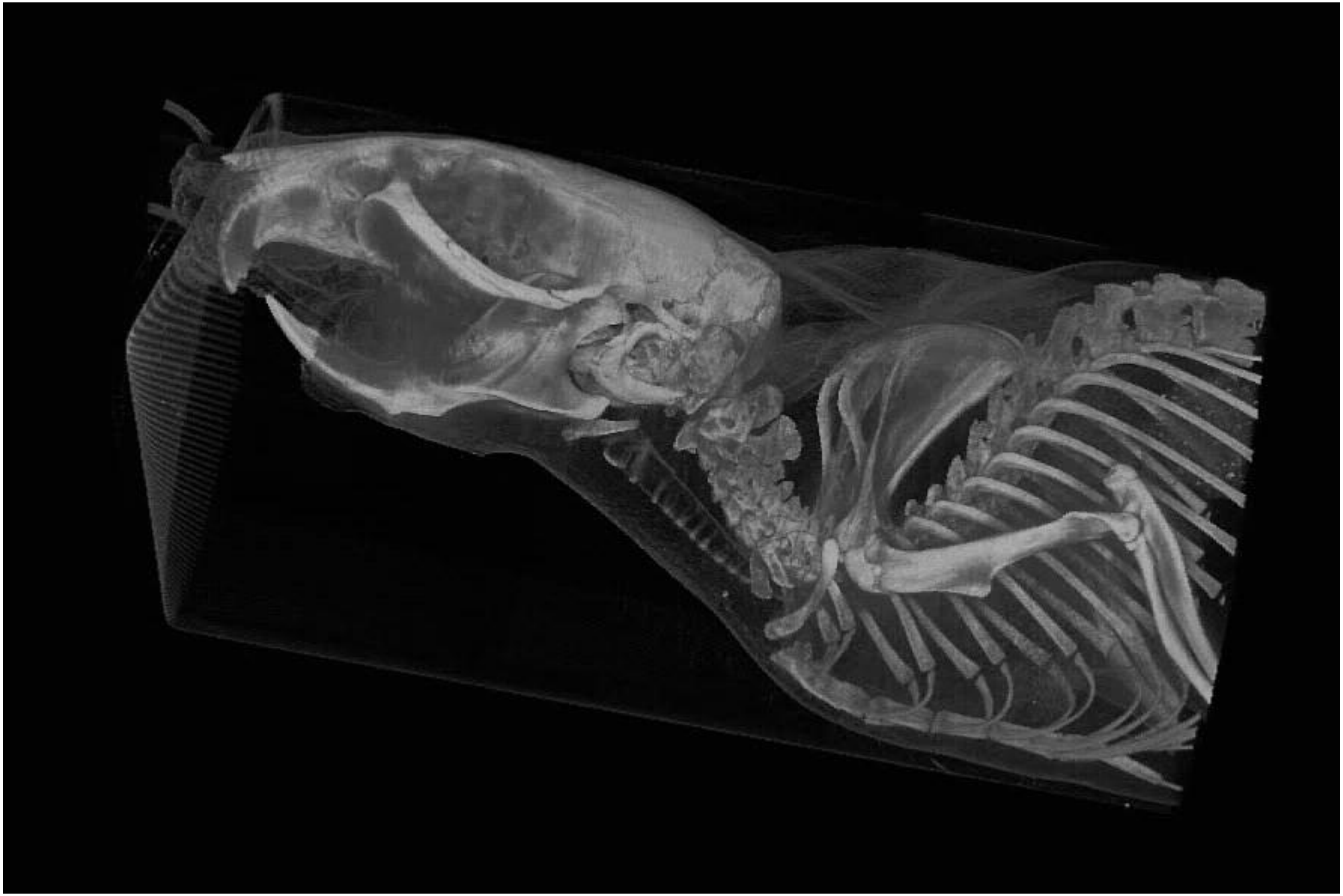
Exploit What Synchrotrons Are Good At

- 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
- Allows studies of better x-ray imaging and developing new methodologies

Synchrotron Radiography

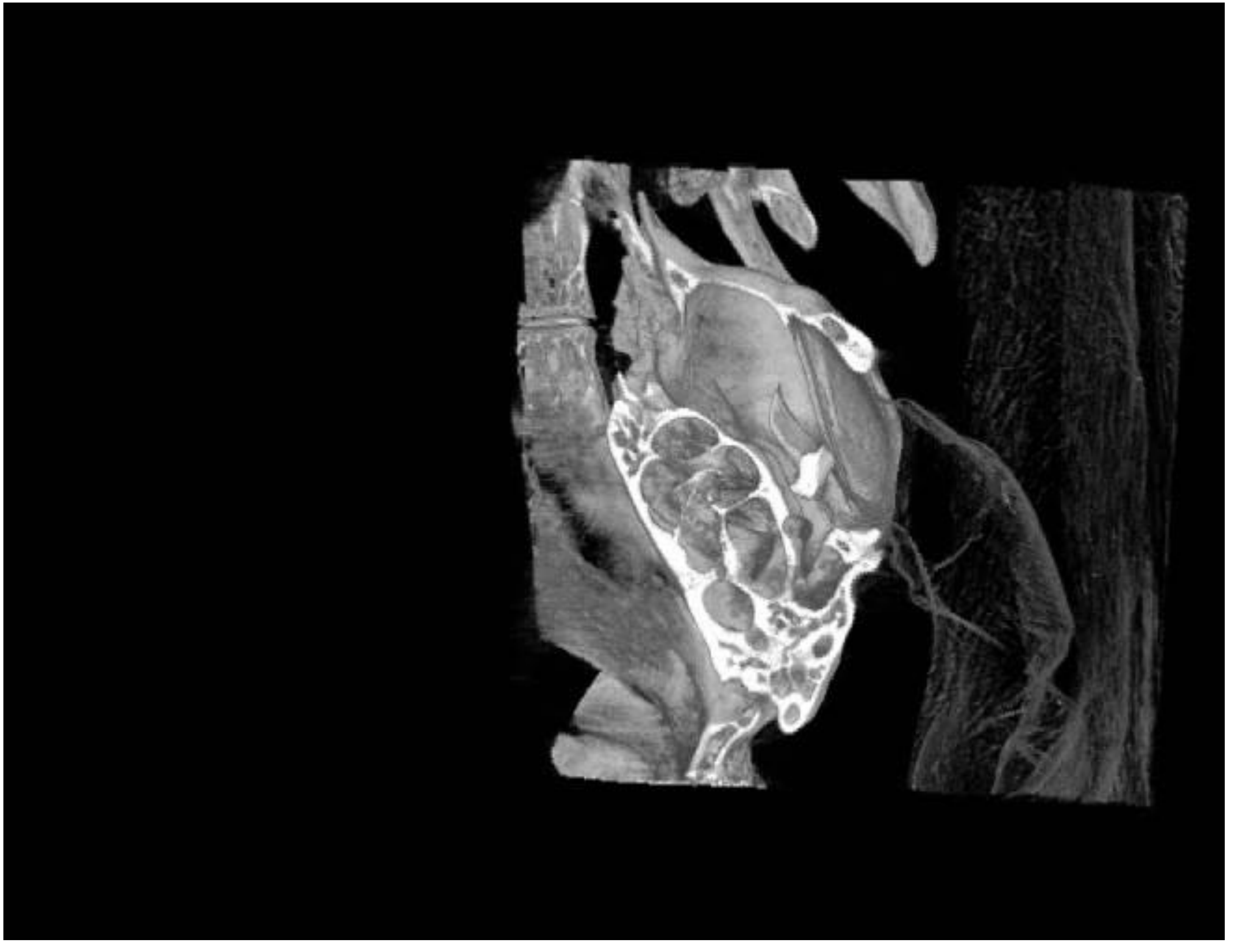


Mouse CT



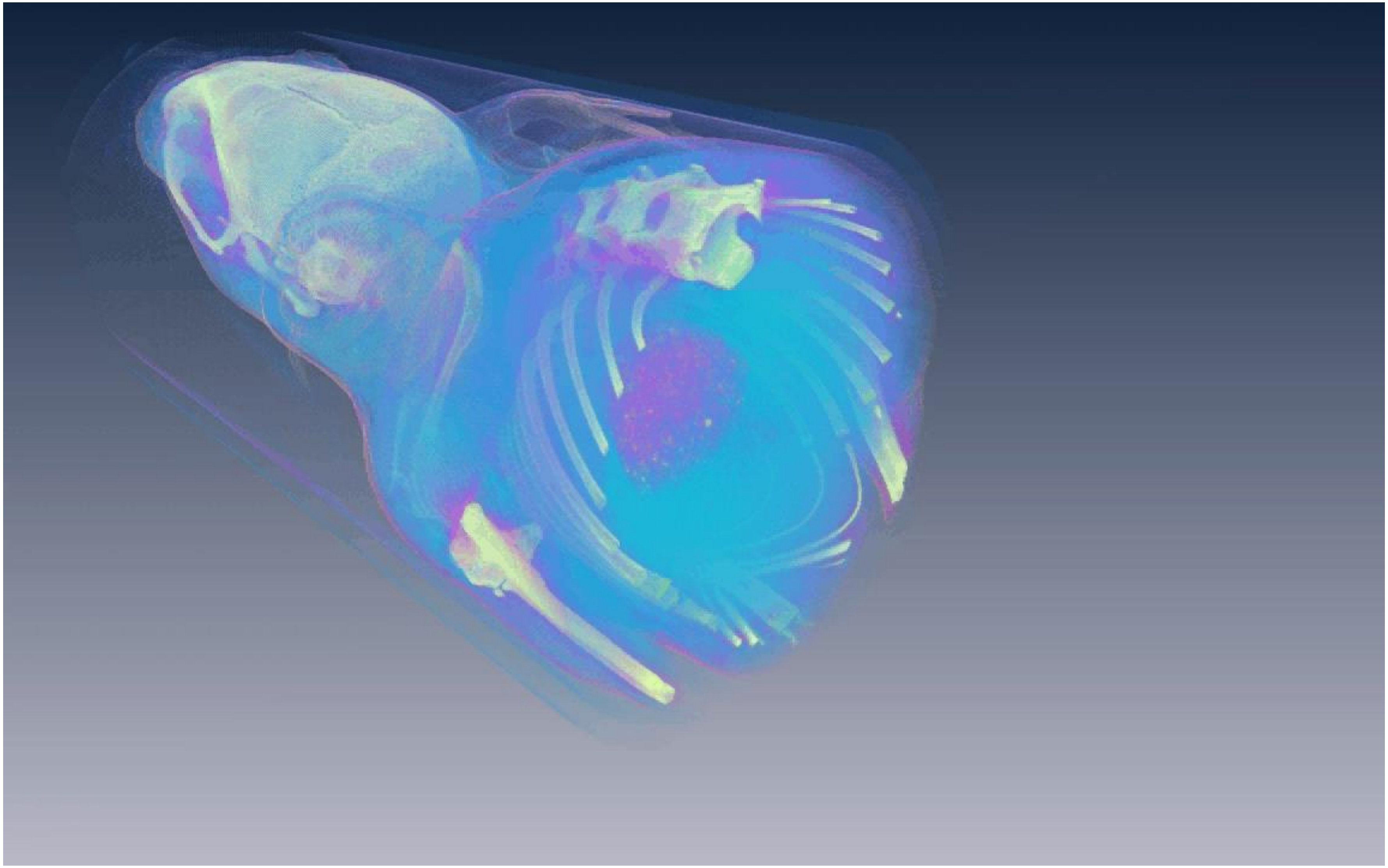
David Parsons and Karen Siu

Mouse Cochlea



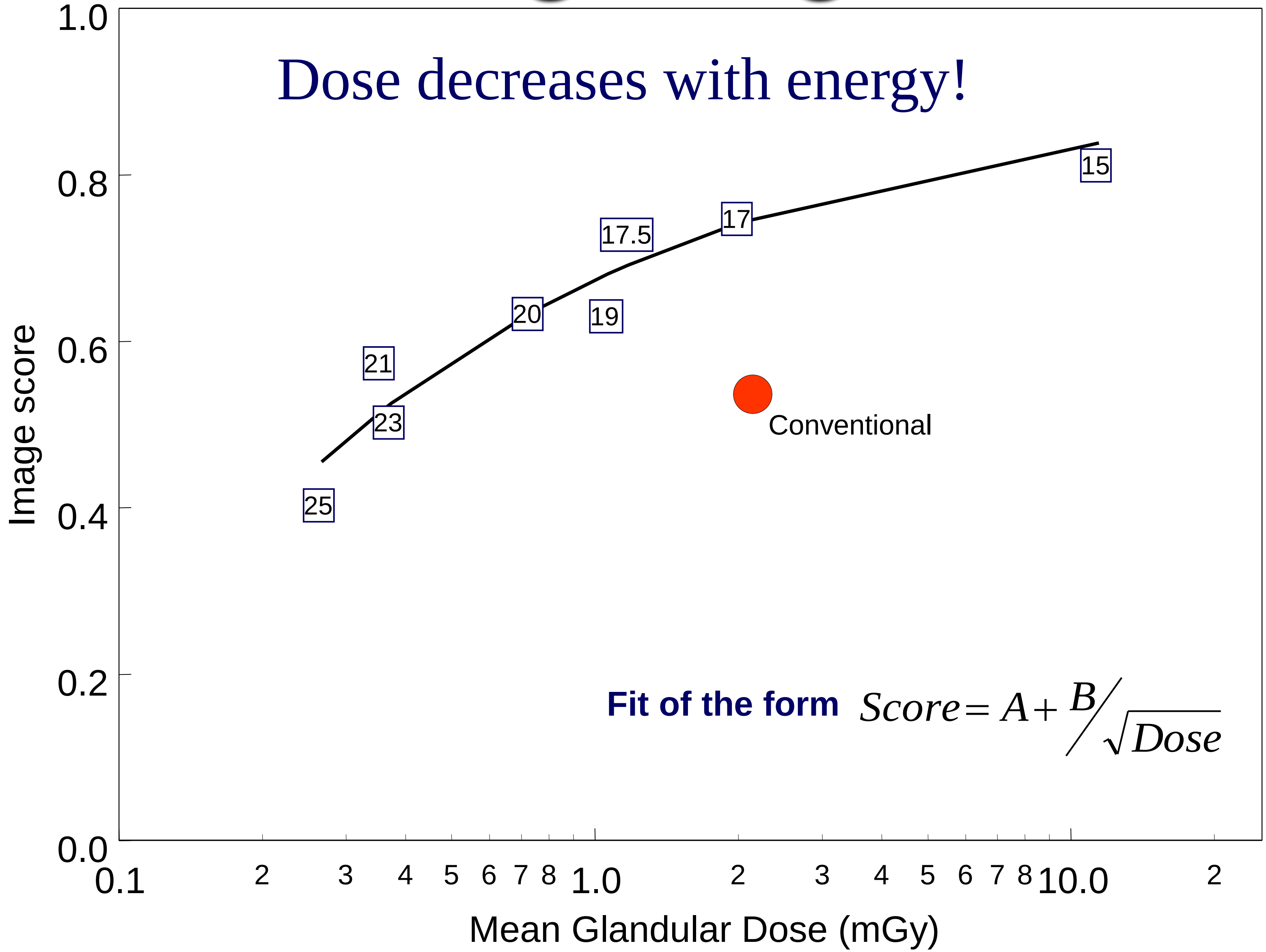
David Parsons and Karen Siu

Mouse Fly Through



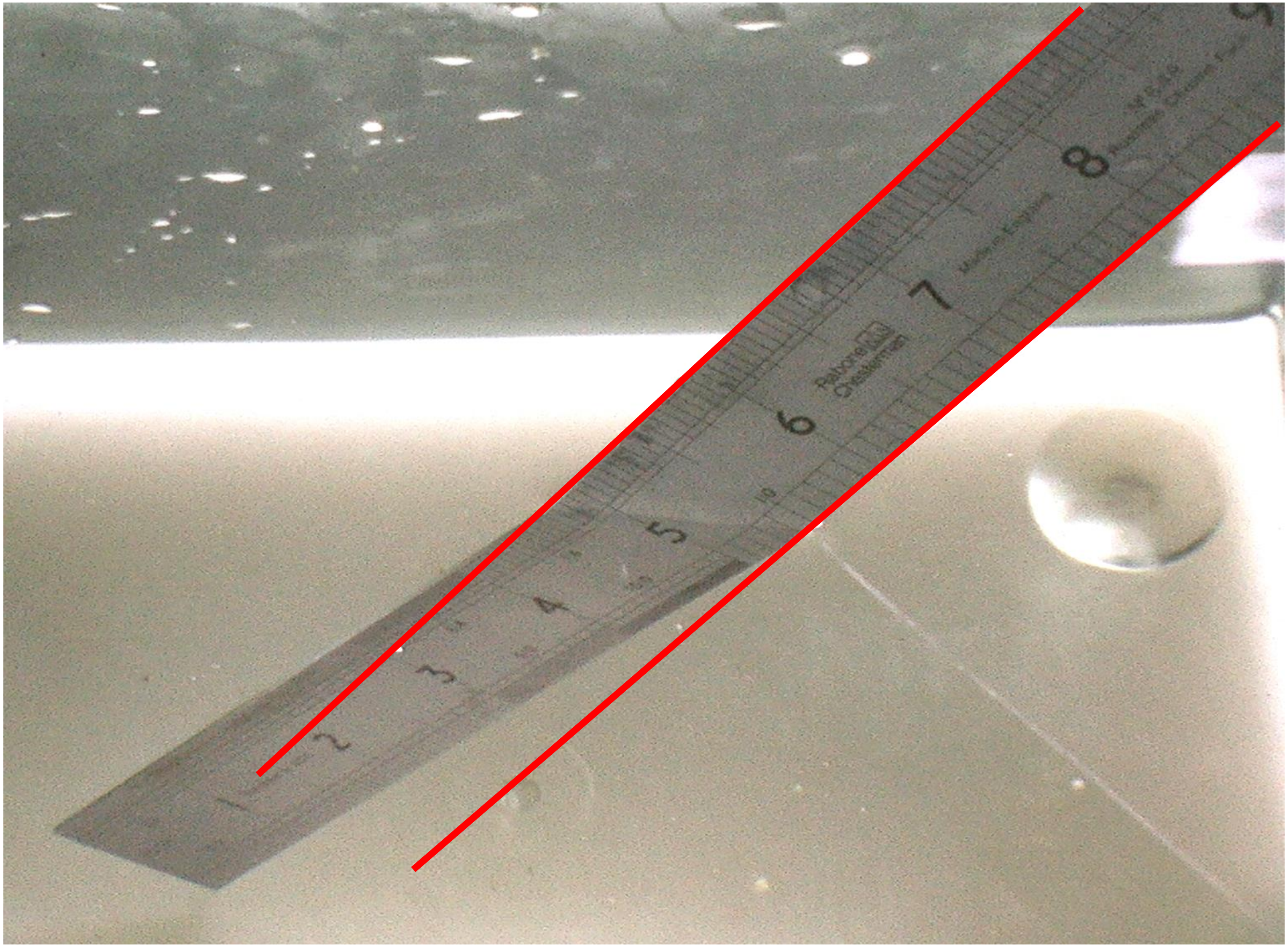
Kaye Morgan, Karen Siu, David Parsons

Slot Scanning Image Scores



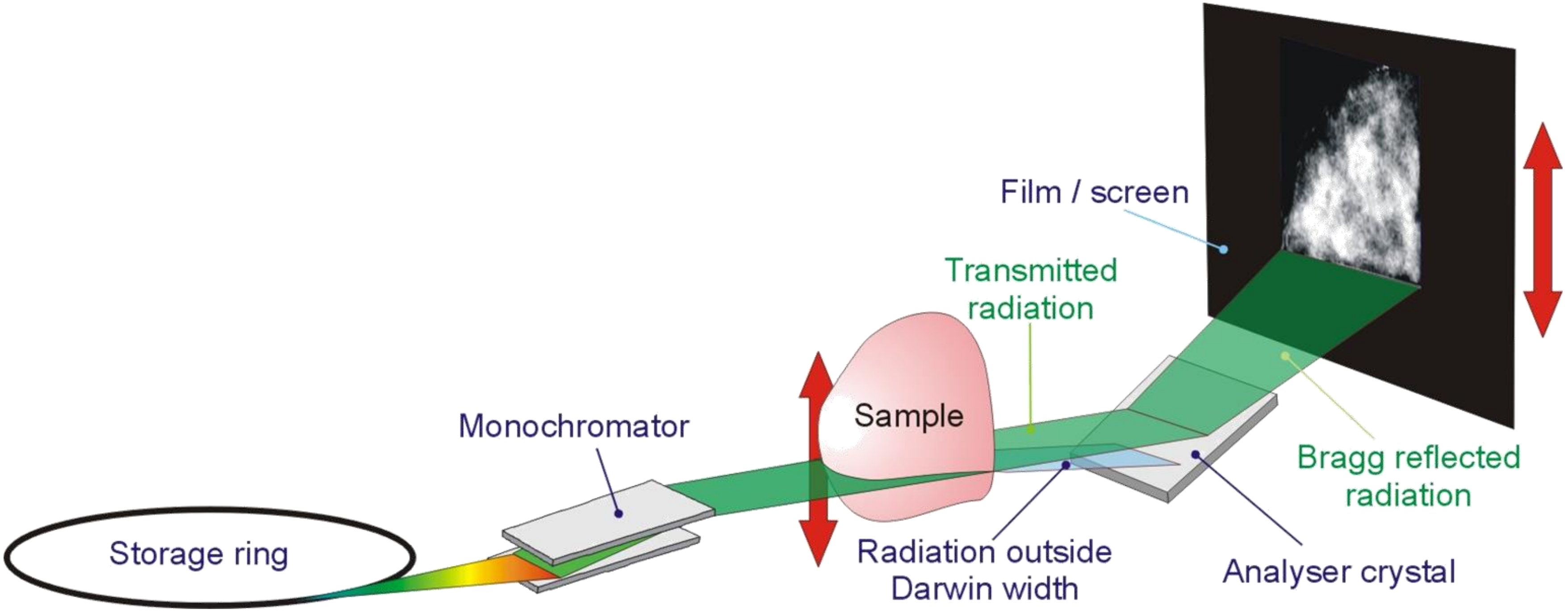
RA Lewis et al SPIE Vol. 4682 (2002) 286-297

Refraction

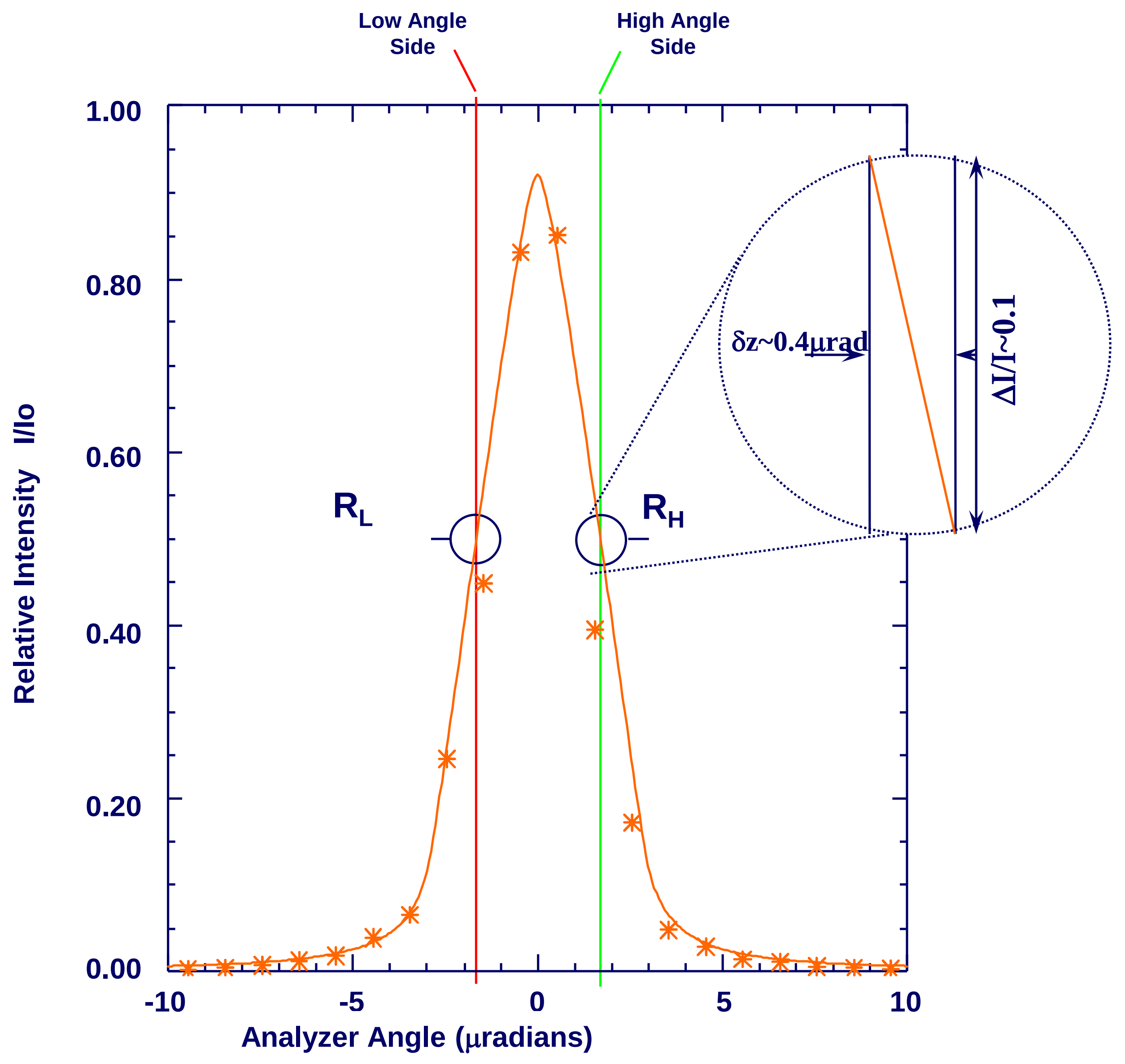


Analyser Based Imaging

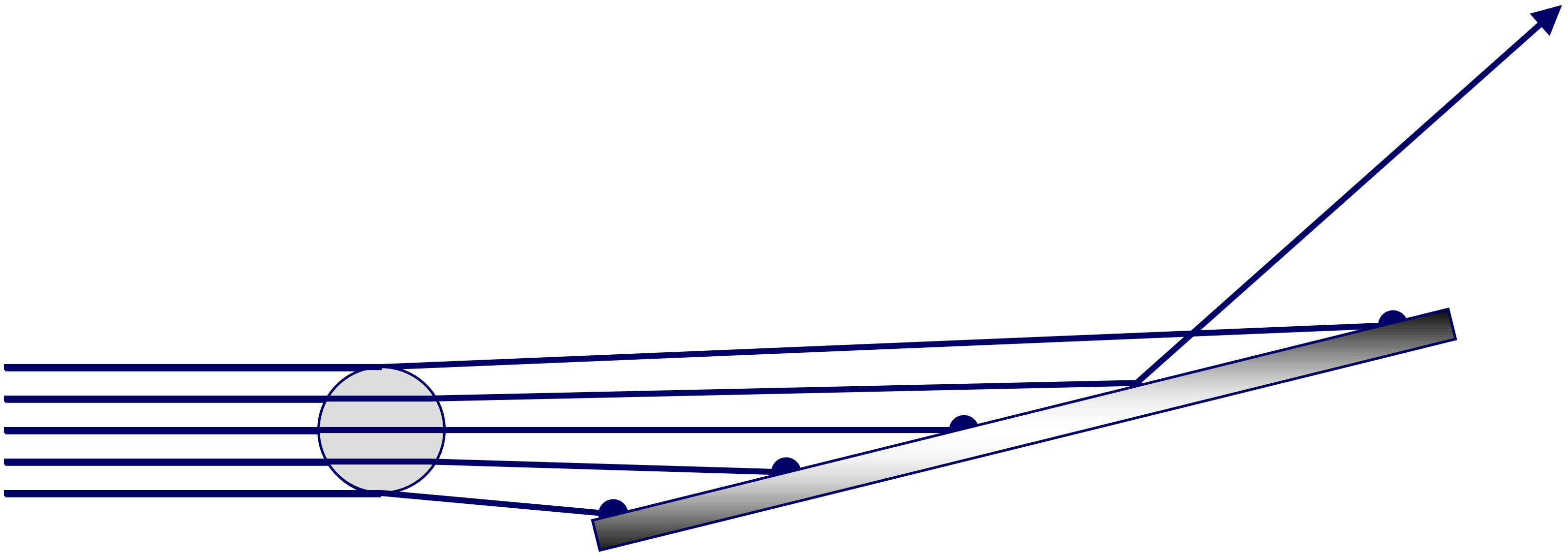
Sometimes called Diffraction Enhanced Imaging



Crystal Rocking Curve

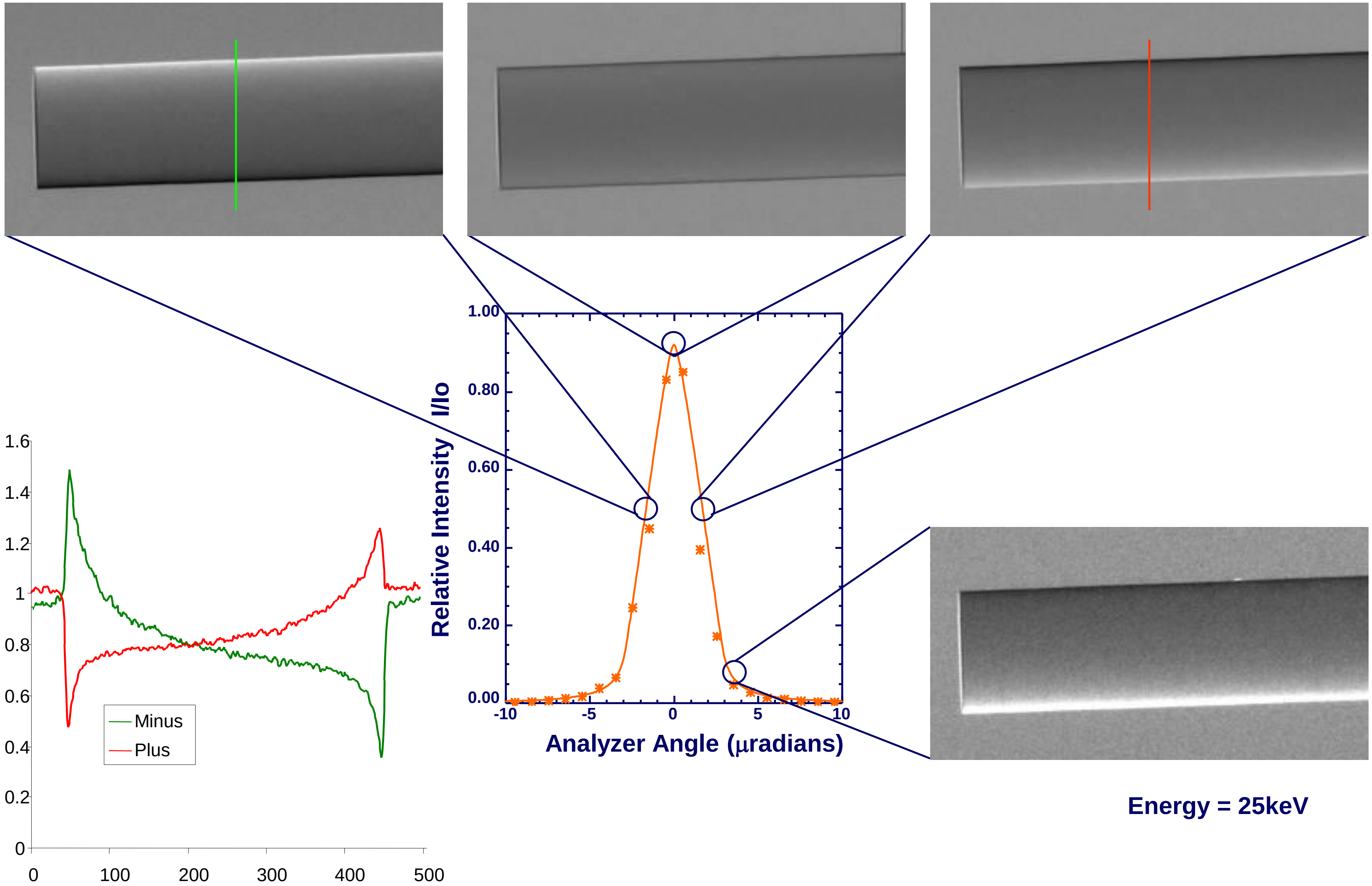


Rocking Curve



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

ABI How it works



Energy = 25keV

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

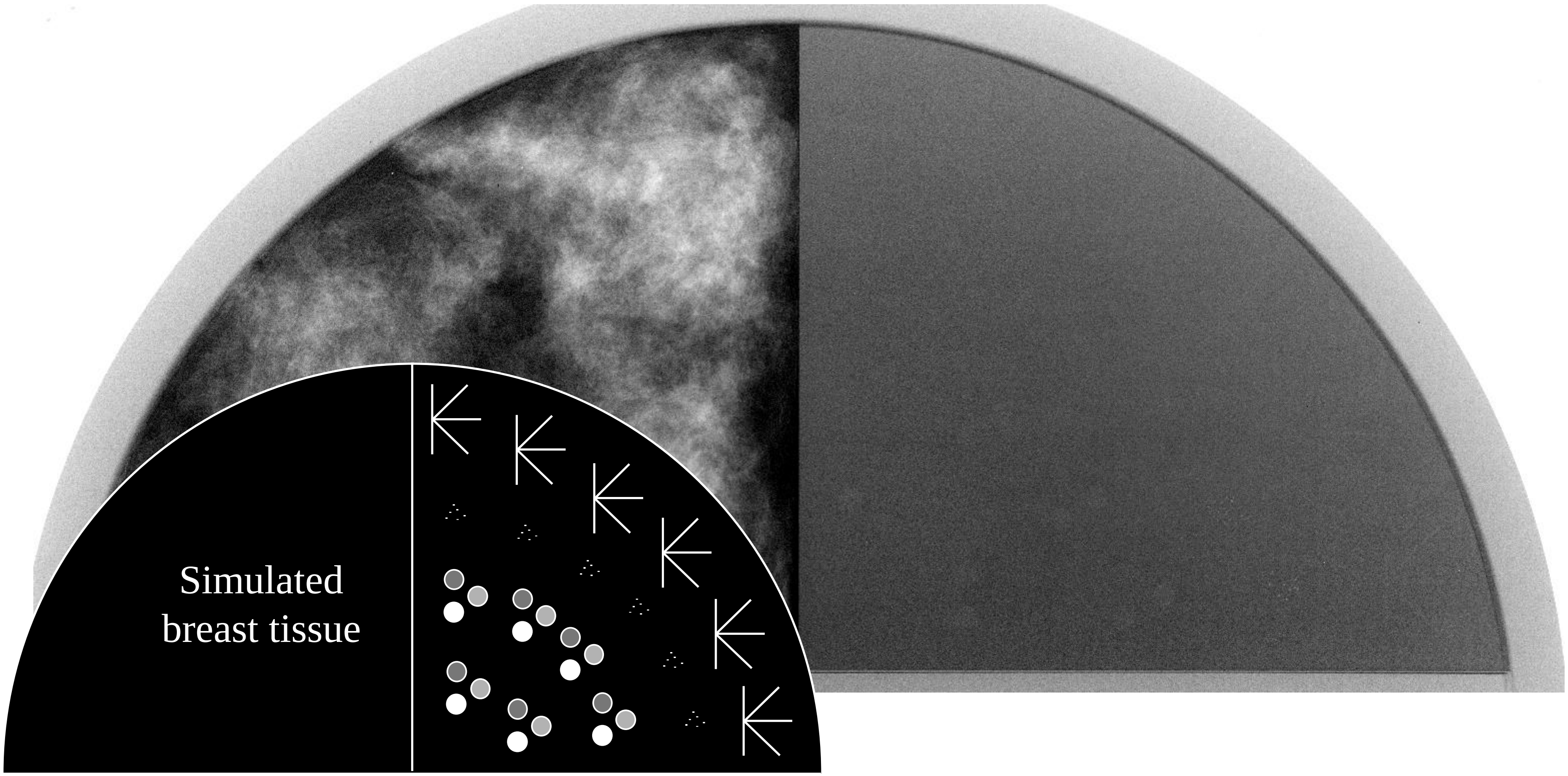
Given

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

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

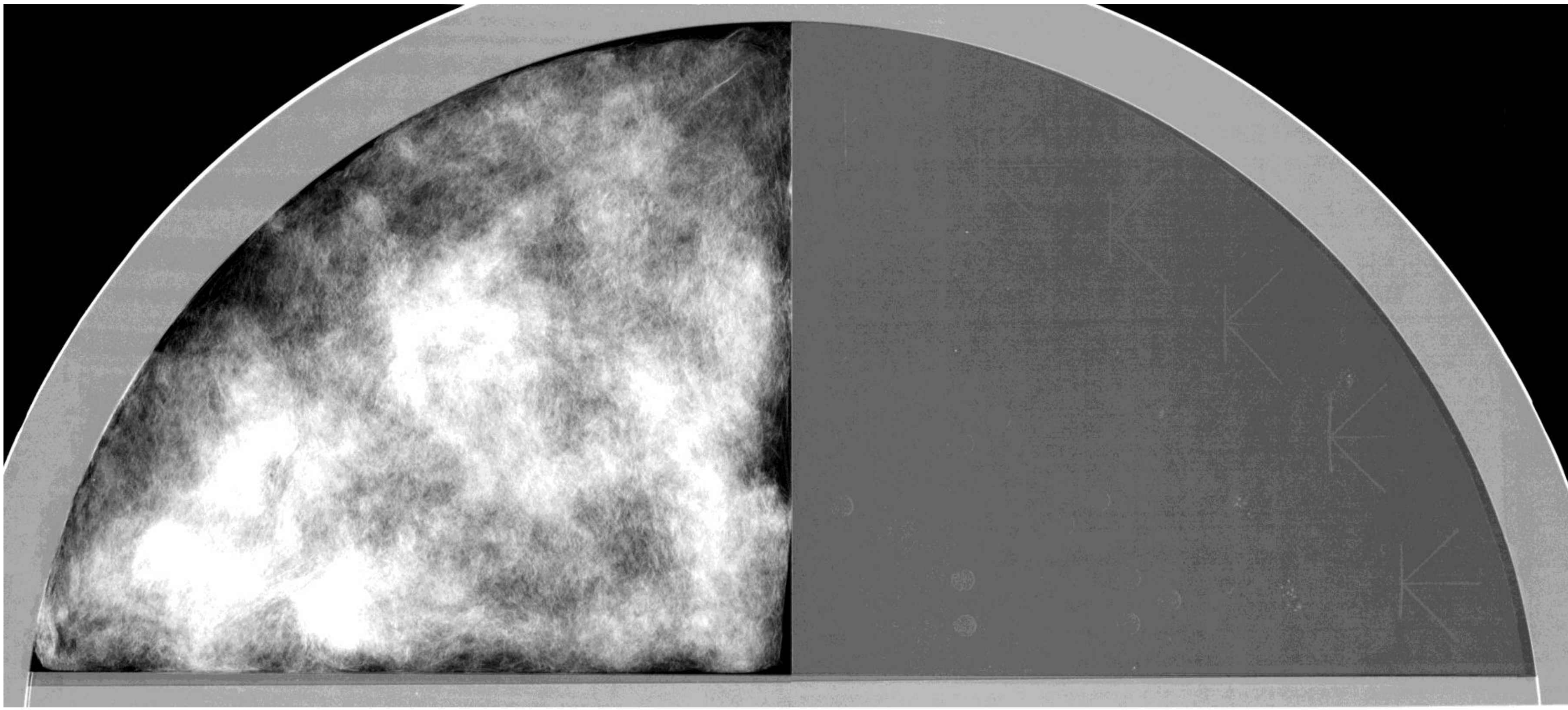
$$\mathrm{Find}\left(I_R, \Delta\theta_Z\right) \rightarrow \begin{pmatrix} \dfrac{Grad_H \cdot I_L - Grad_L \cdot I_H}{Grad_H \cdot R_L - Grad_L \cdot R_H} \\ \dfrac{I_H \cdot R_L - I_L \cdot R_H}{Grad_H \cdot I_L - Grad_L \cdot I_H} \end{pmatrix}$$

TORMam Conventional



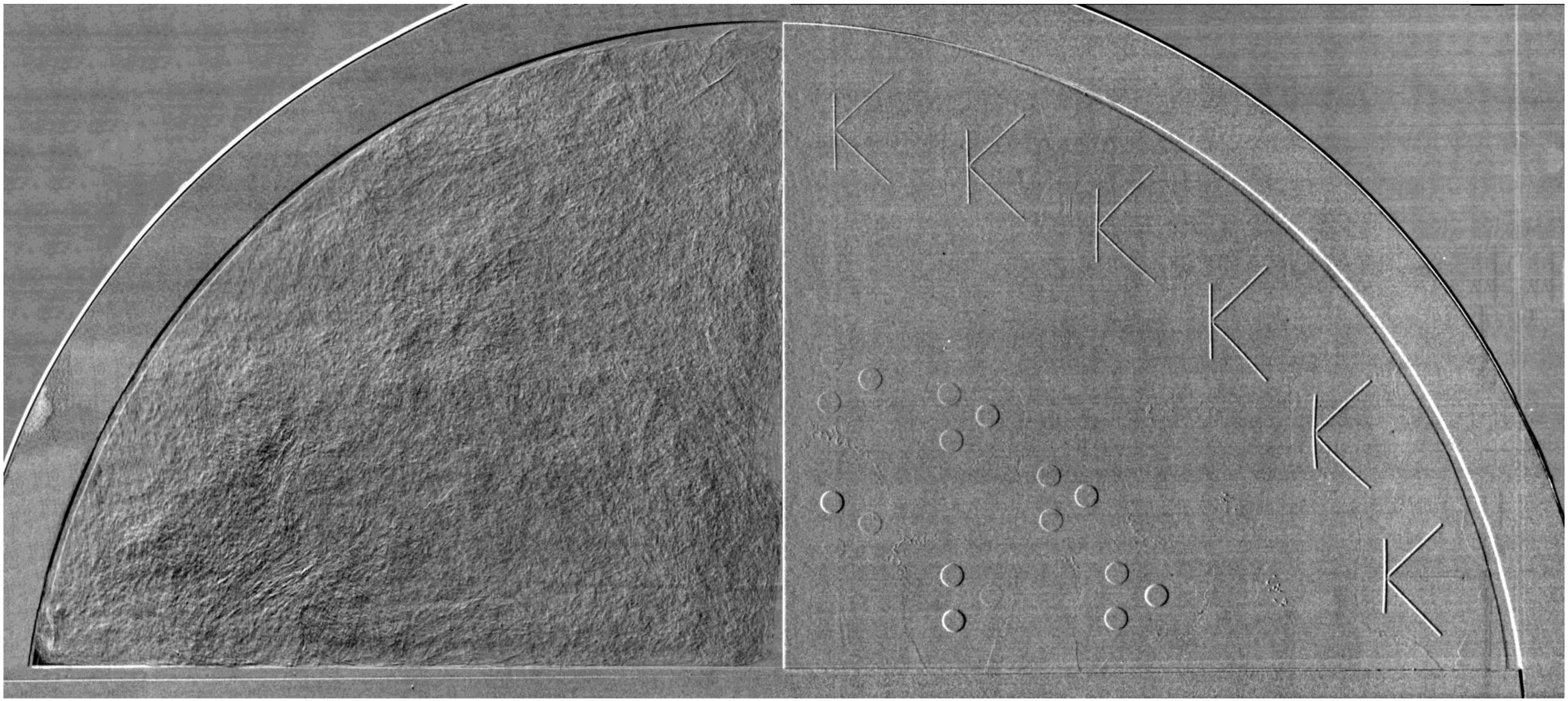
Spectrum = Mo:Mo 28kVp

TORMAM Peak



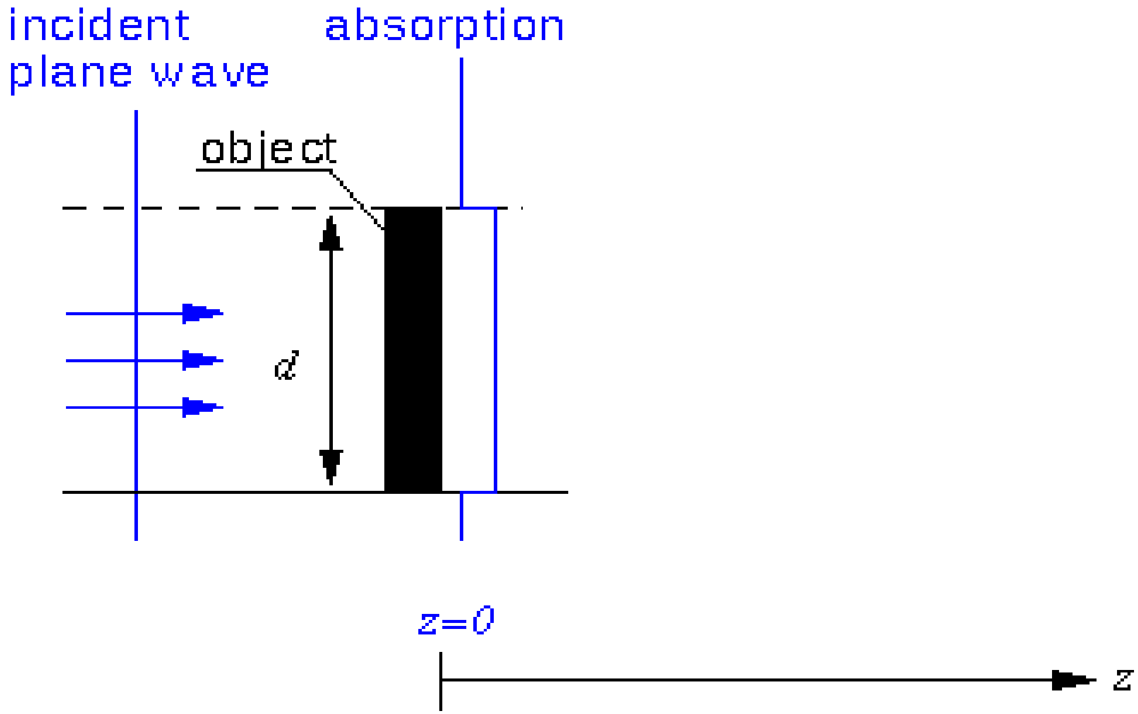
Energy = 20keV

TORMAM Refraction



Energy = 20keV

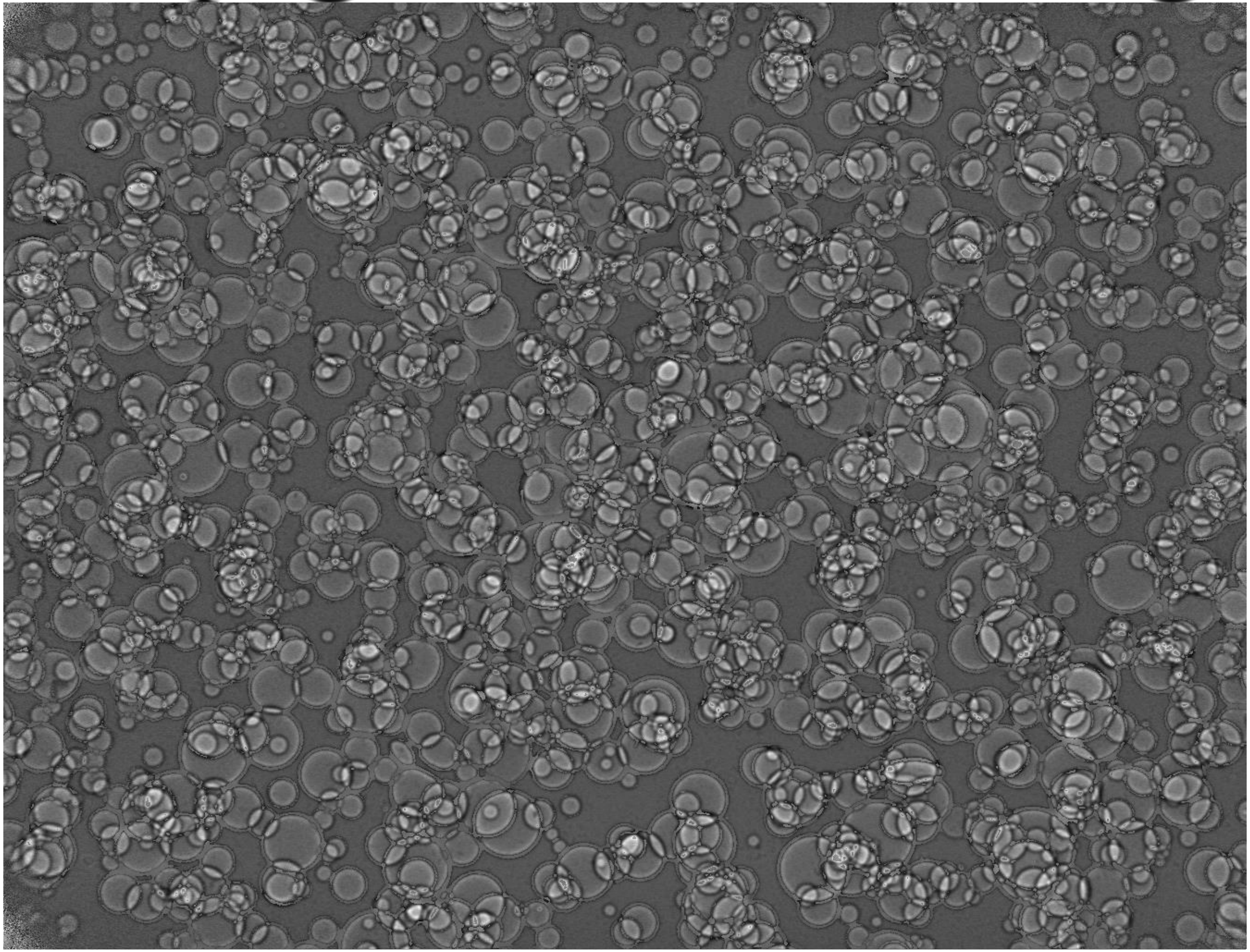
Phase Contrast



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

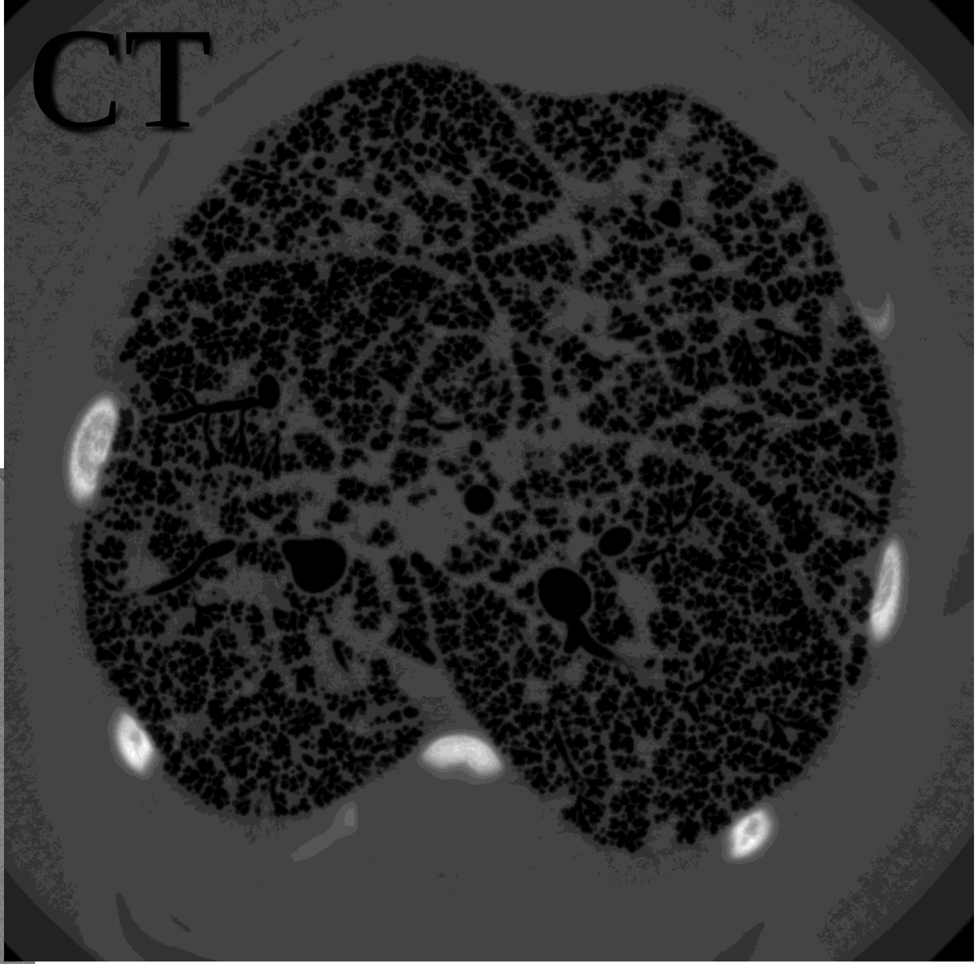
- **Contact:** $N_F >> 1$ **Geometric approximation**
  - The intensity distribution is a pure absorption image.
- **Near field:** $N_F >> 1$ **Geometric approximation**
  - Contrast is given by sharp changes in the refractive index, i. e. at interfaces.
- **Intermediate field:** $N_F \sim 1$ **Fresnel 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

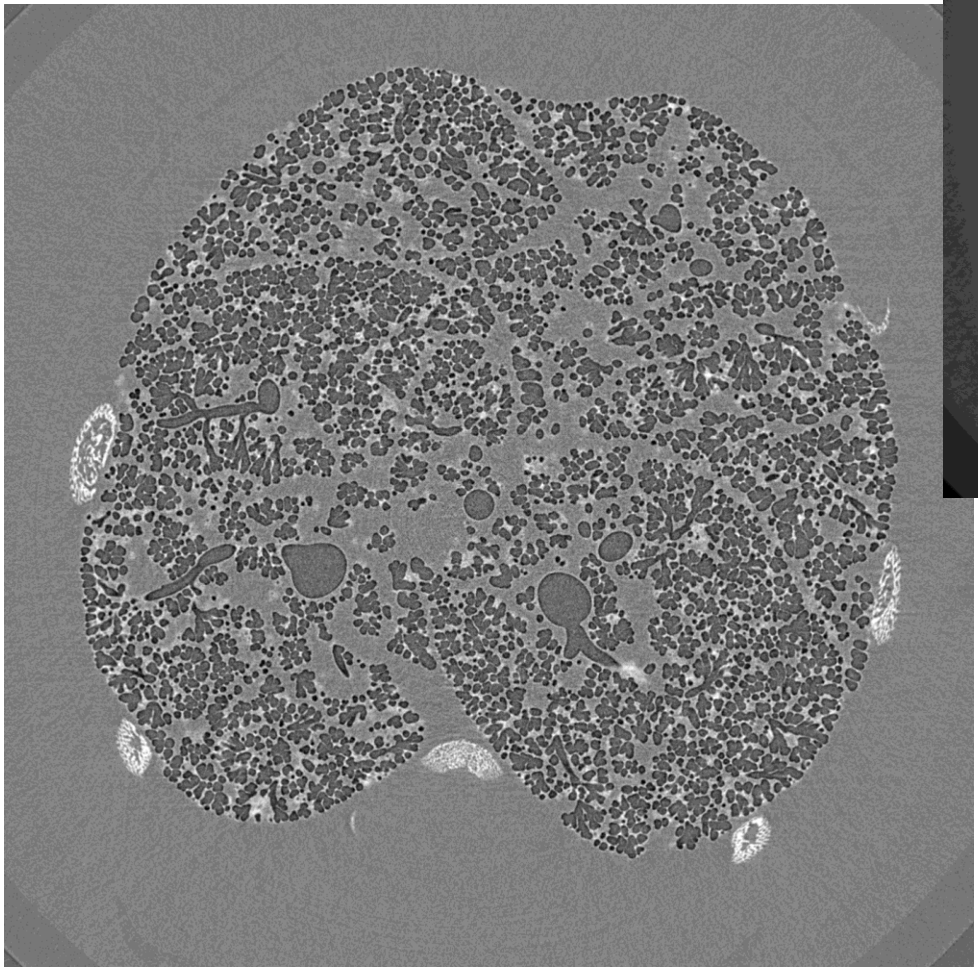
Propagation Based Imaging



147cm

Phase Contrast CT

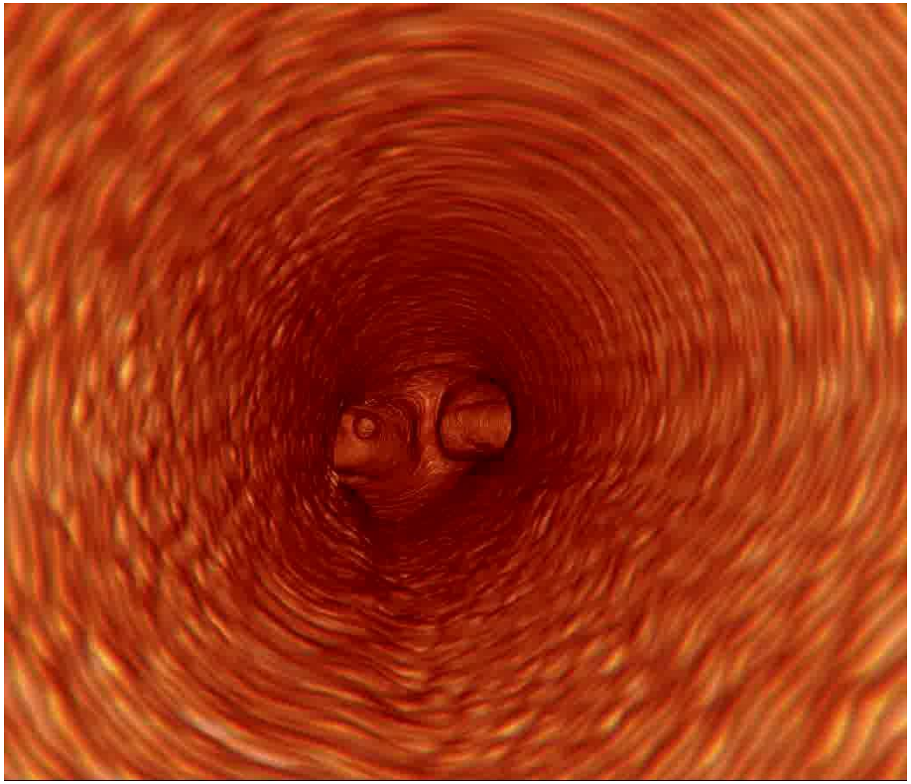




Lungs of newborn rabbit
Propagation distance = 1m
Energy = 24 keV

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

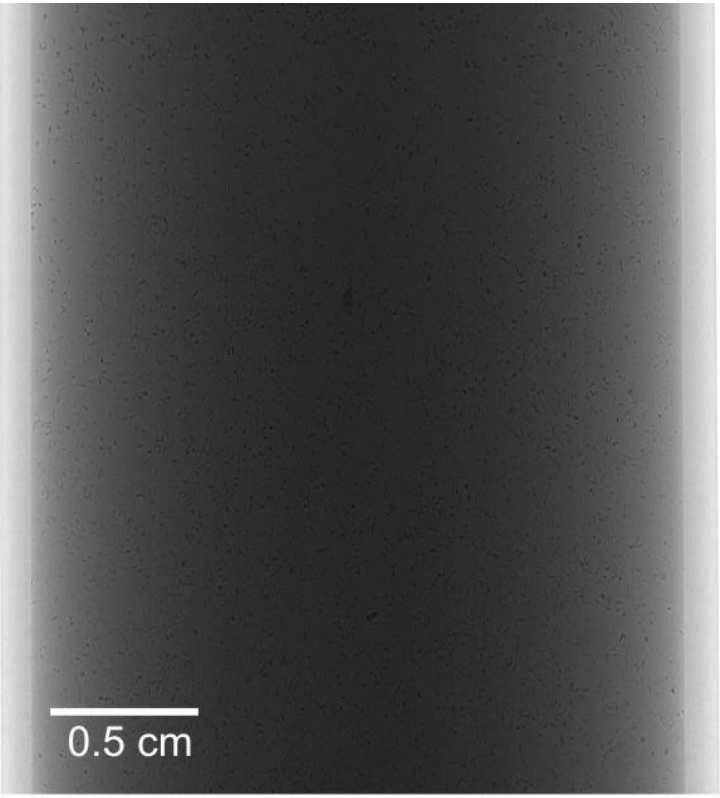
Phase Contrast CT



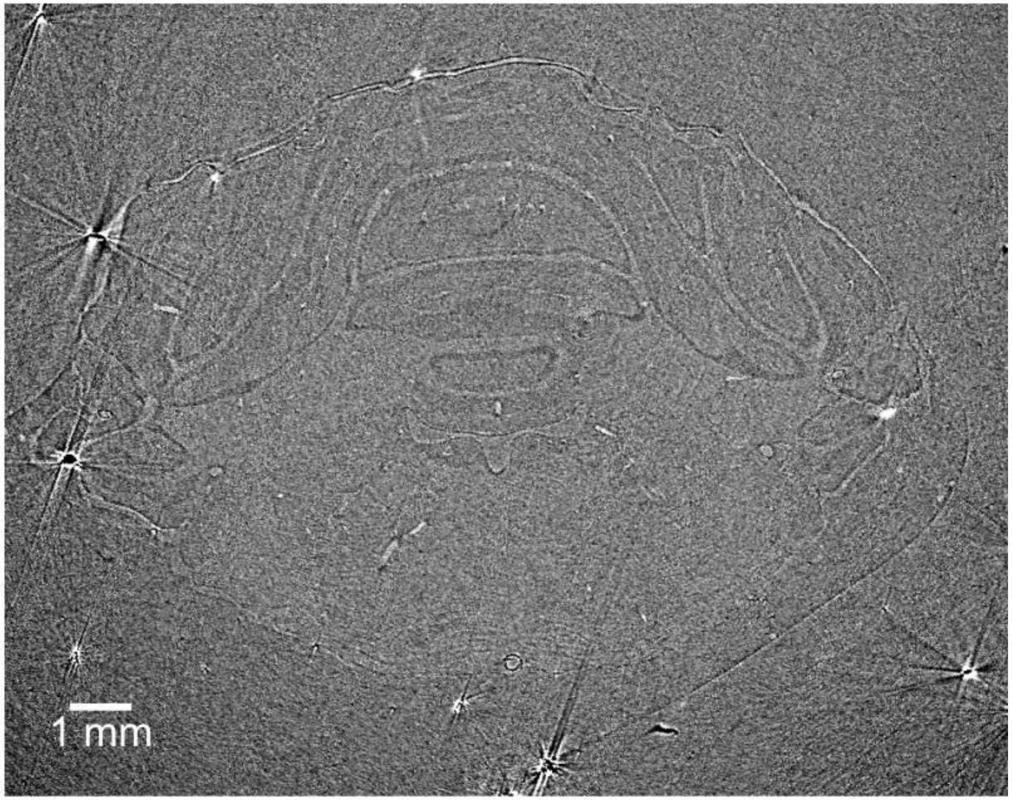
- SNR increased 10x, enabling high quality visualization

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

Rat Brain in agarose gel



(a)

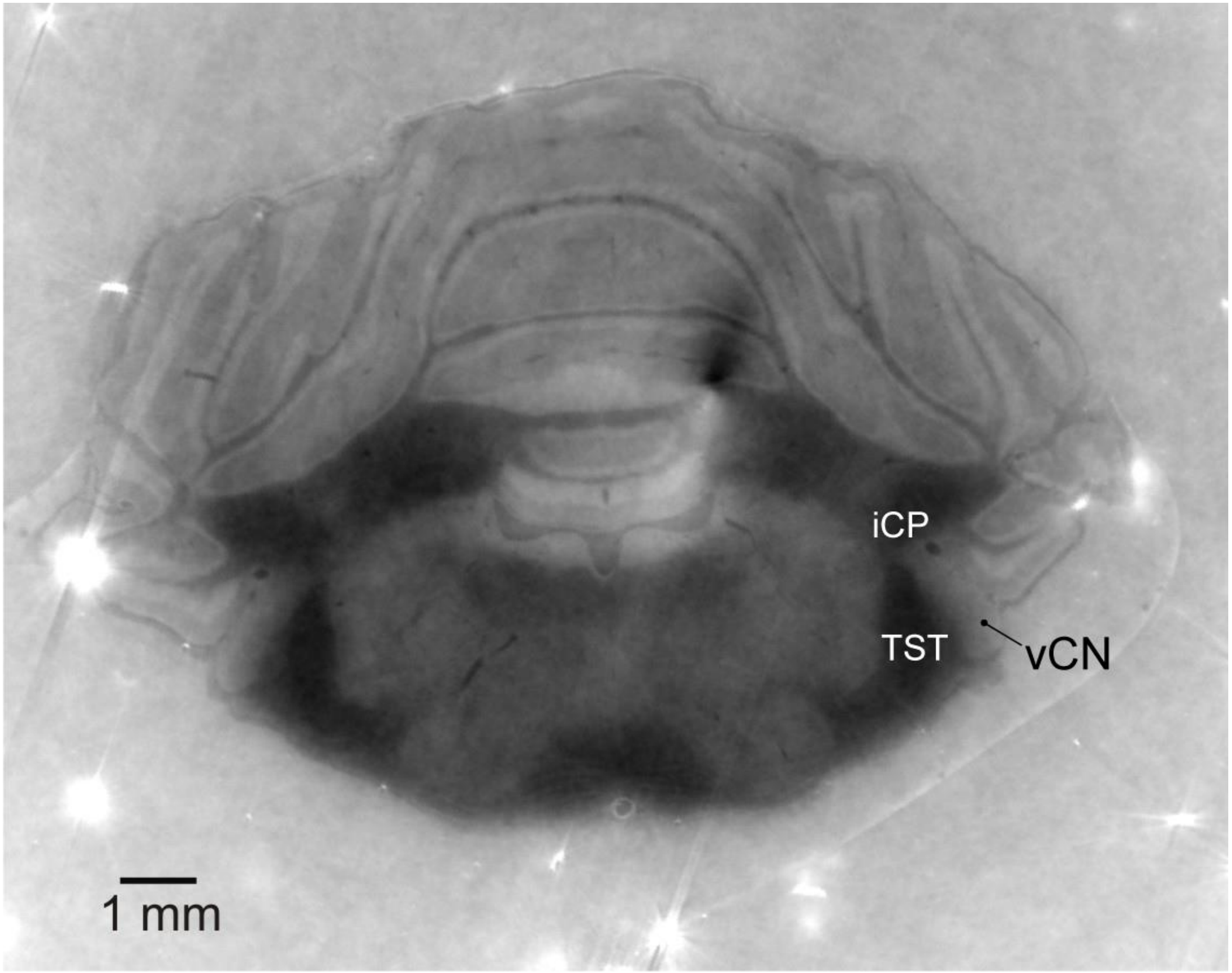


(b)

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*.

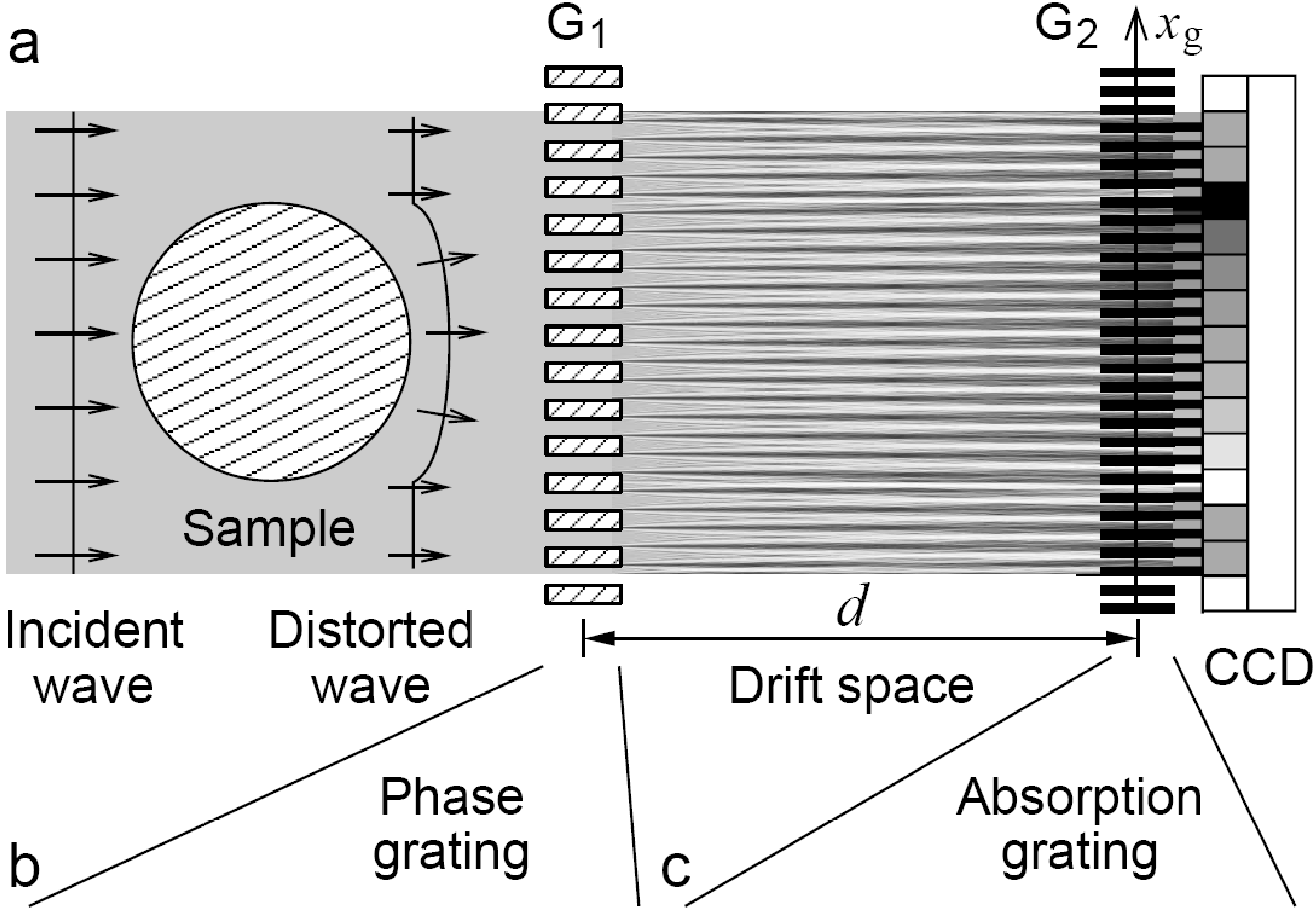
Rat Brain in agarose gel



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

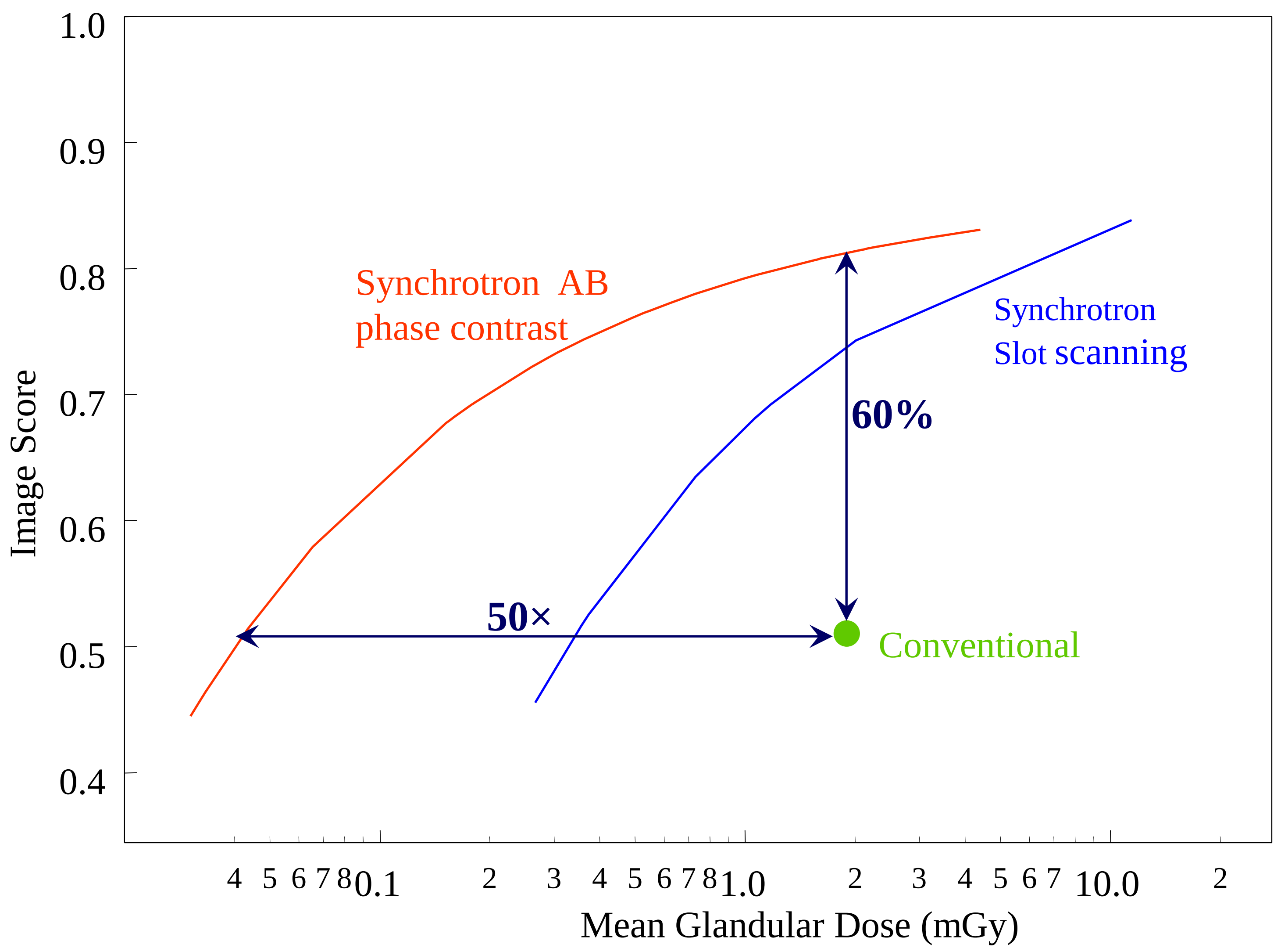
Hoshino M et al Biology Open 1, 269–274

Exploit What Synchrotrons Are Good At

- Synchrotrons allow fantastic spatial resolution
- But what about the dose?

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

Phase Contrast Dose Advantage



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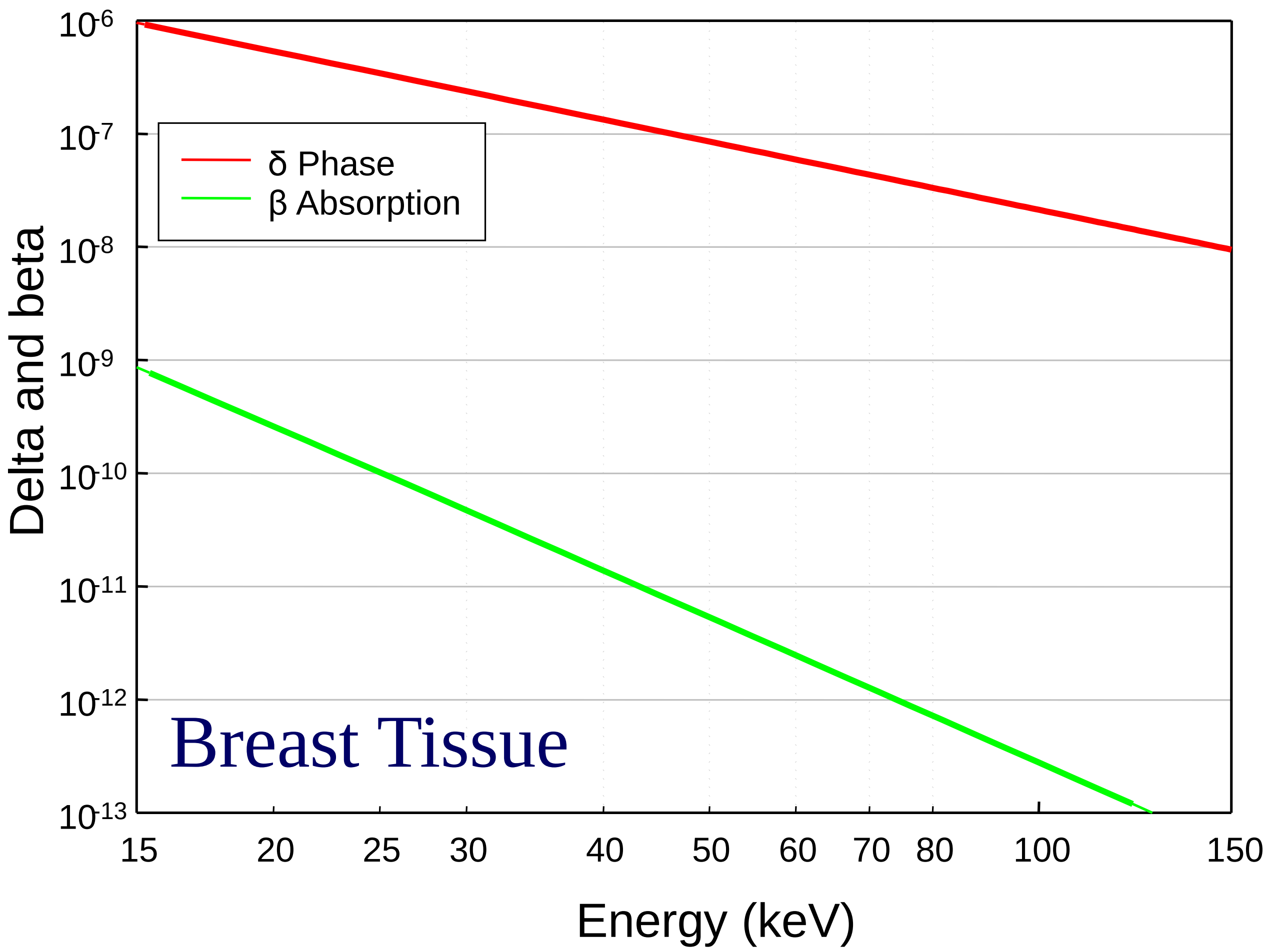
Complex Refractive Index

- 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

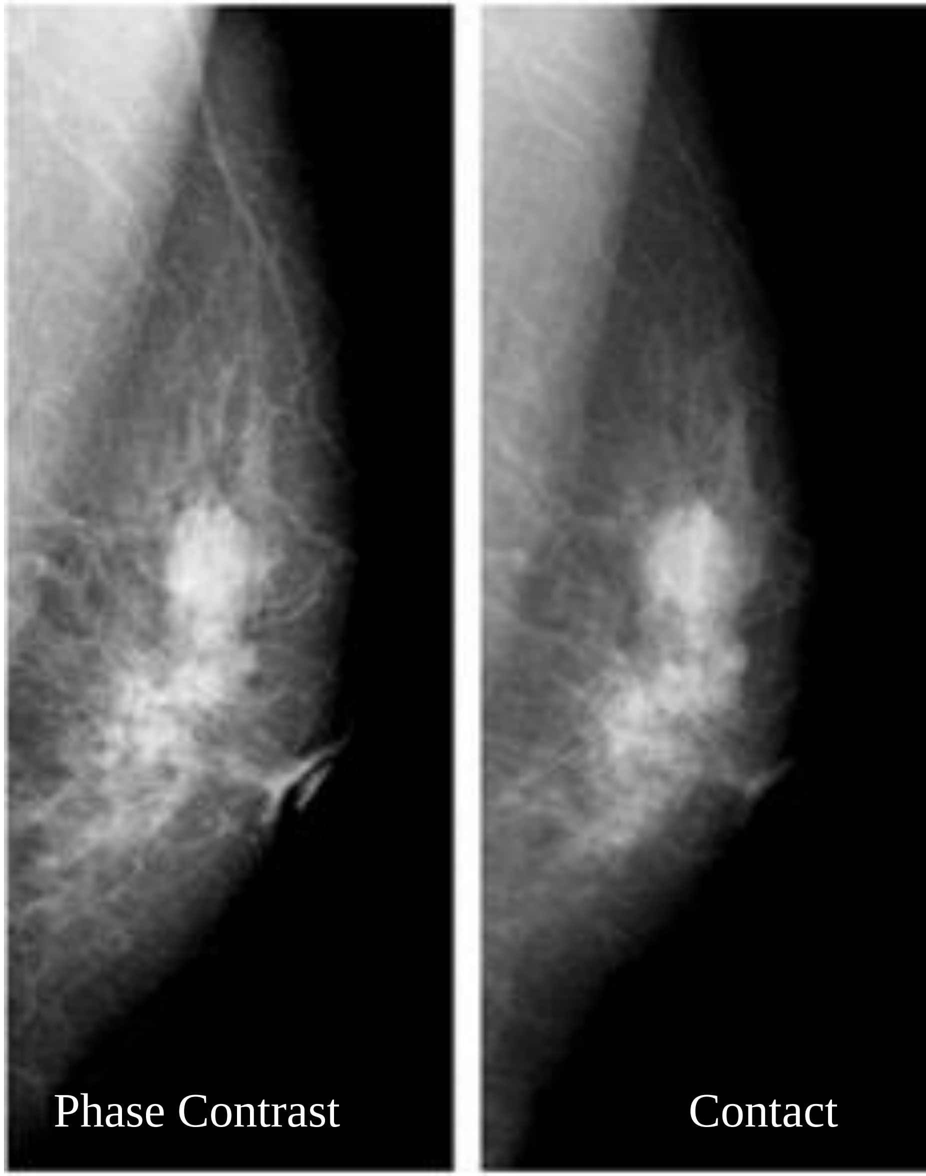
Nb.
$\delta \sim 1000\ \beta$
$\delta \sim E^{-2}$
$\beta \sim E^{-4}$

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.

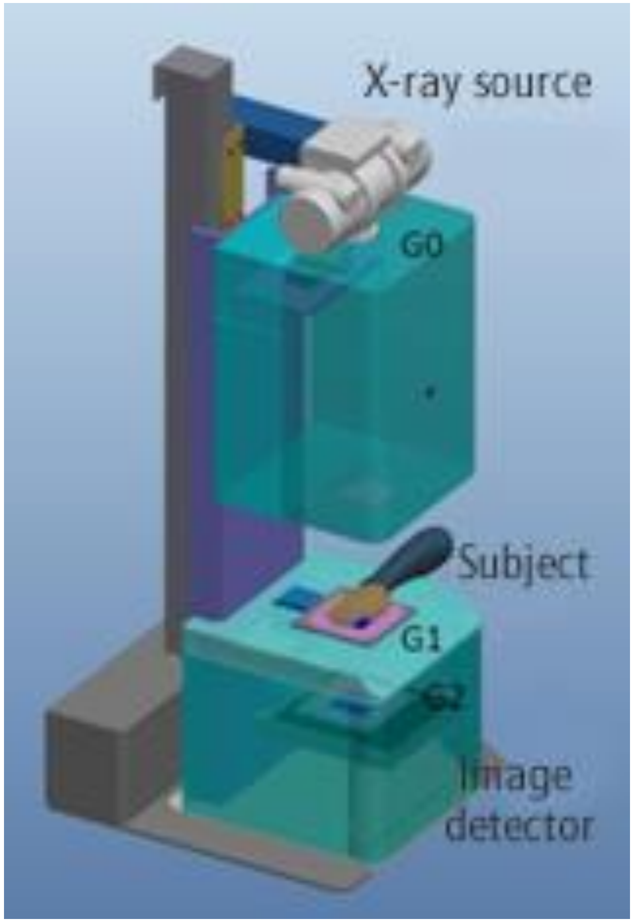
Phase Contrast in the Clinic

Konica Minolta REGIUS PureView



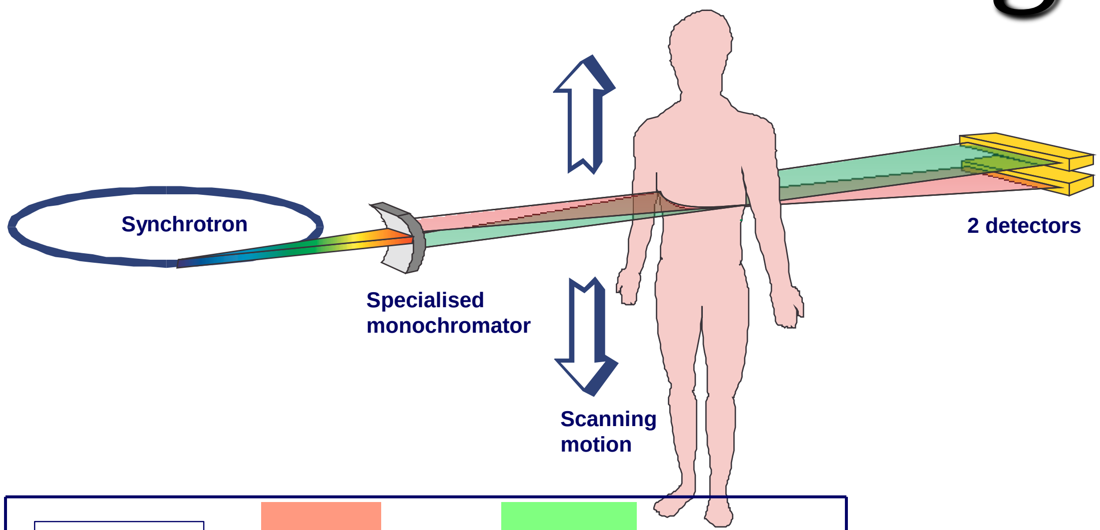
Phase Contrast in the Clinic

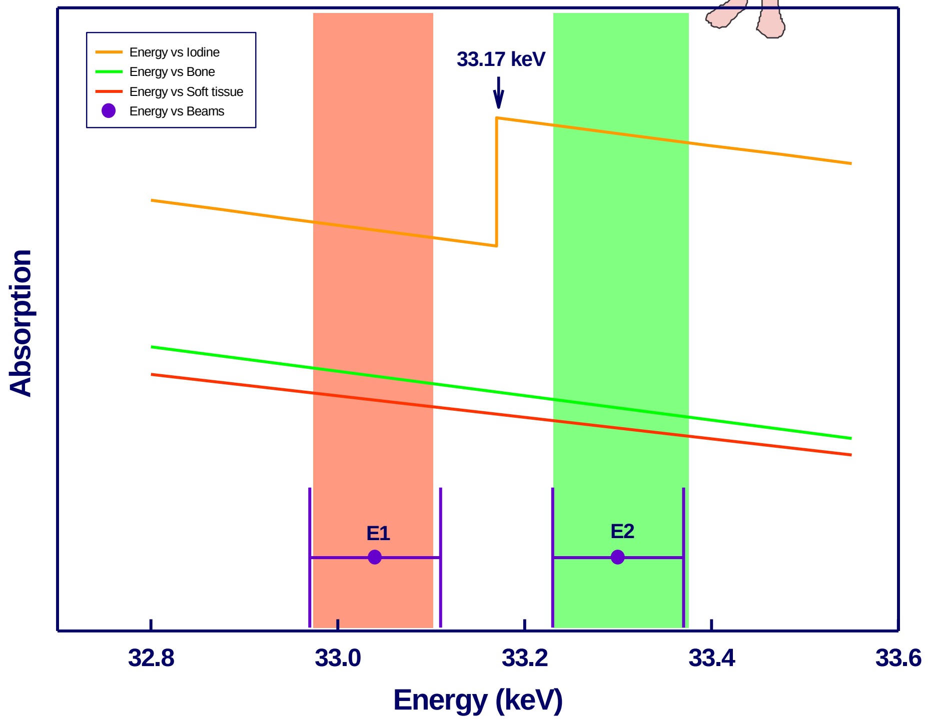
Konica Minolta Research & Development



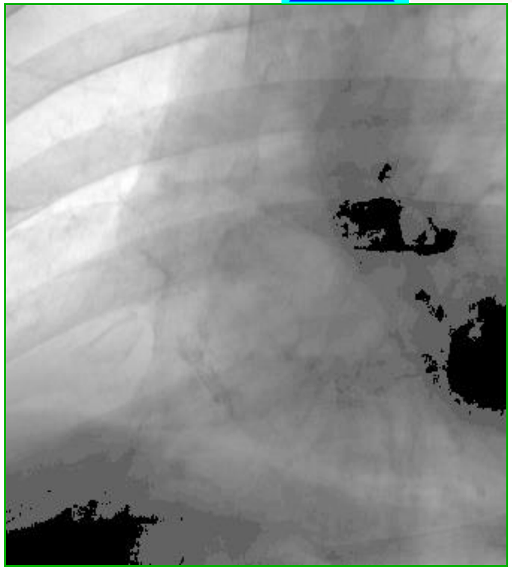
http://www.konicaminolta.com/about/research/special_healthcare/talbotlau.html

Subtraction Radiography

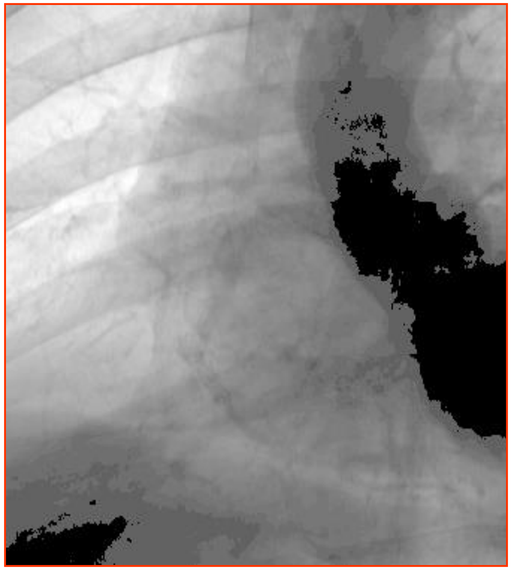




High

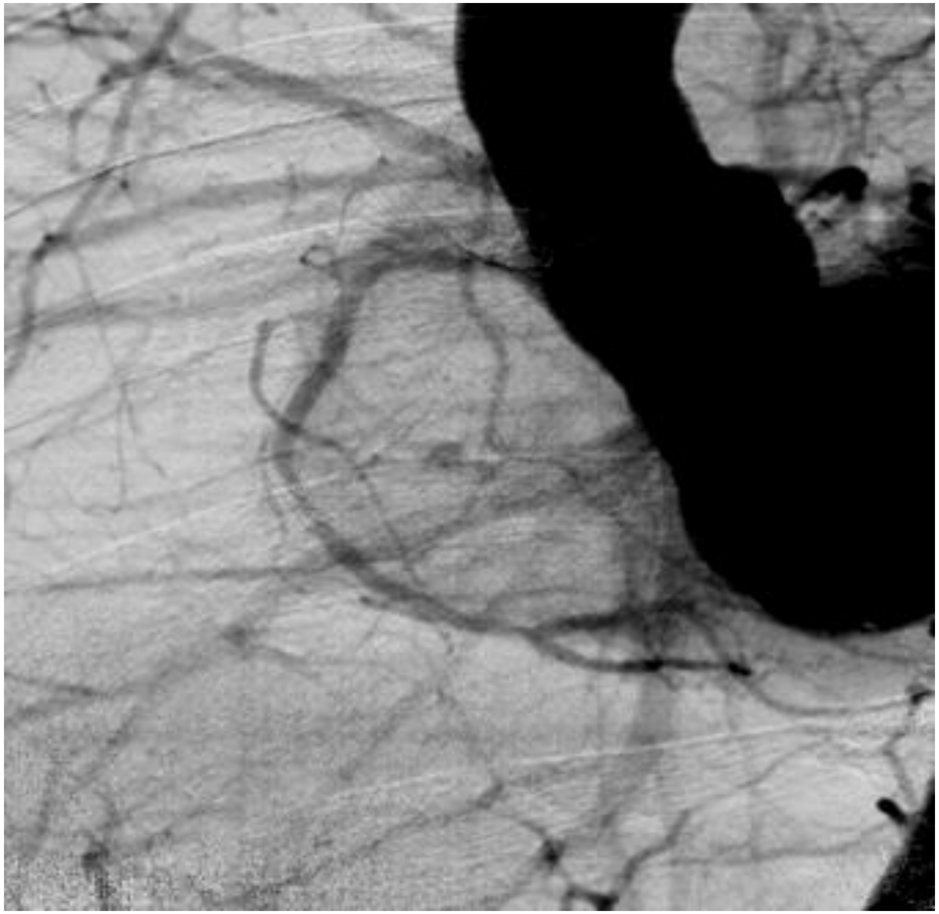


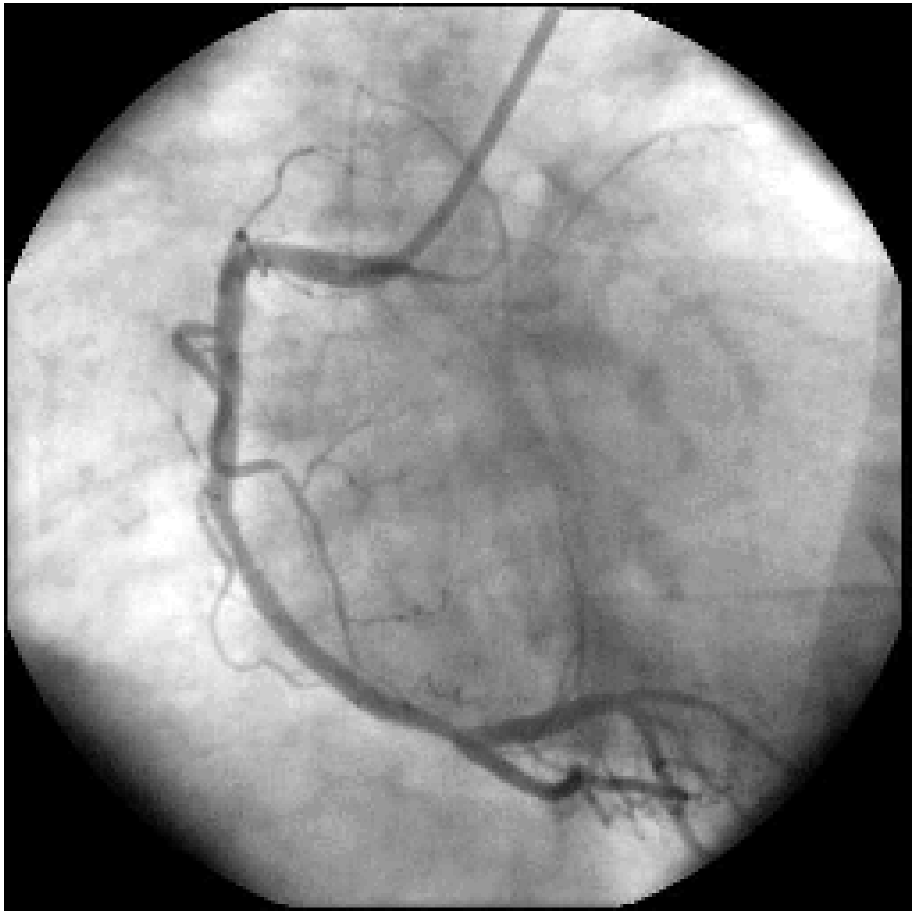
Low



W. Thomlinson et al ESRF

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





Synchrotron IV injection
n.b. 2 – LAO 40

Conventional angiography
Intra arterial injection

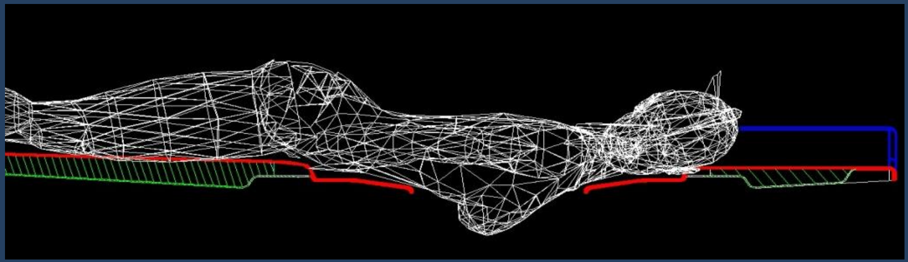
Clinical Mammography at ELETTRA (Trieste, Italy)

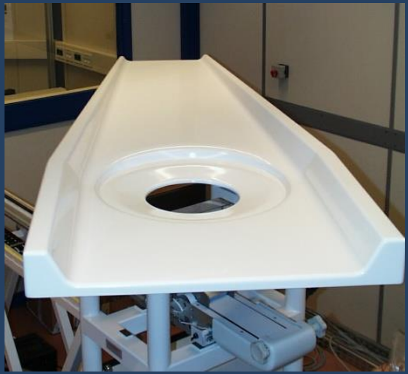
Aim of the study: to prospectively evaluate on a limited number of selected patients the diagnostic contribution of SR Phase Contrast mammography in patients with doubtful or suspicious breast lesions identified at the conventional mammography in the Hospital

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





THE COLLABORATION

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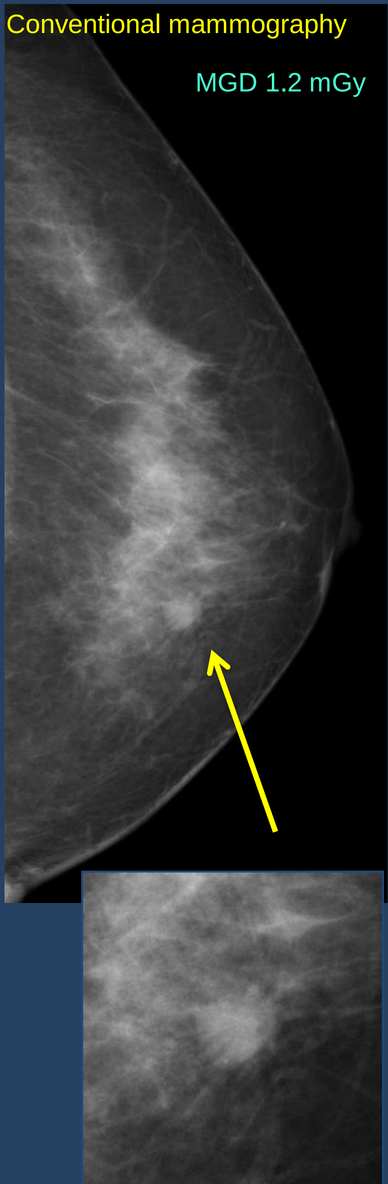
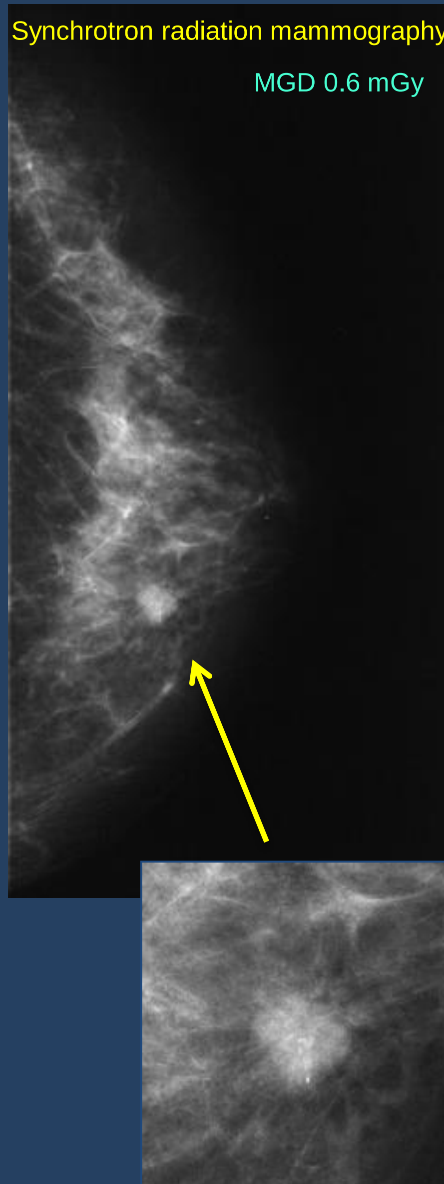
Clinical Mammography at ELETTRA (Trieste, Italy)





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)

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
- Mammography
  - Clinical program proves synchrotron is better
- But………..

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

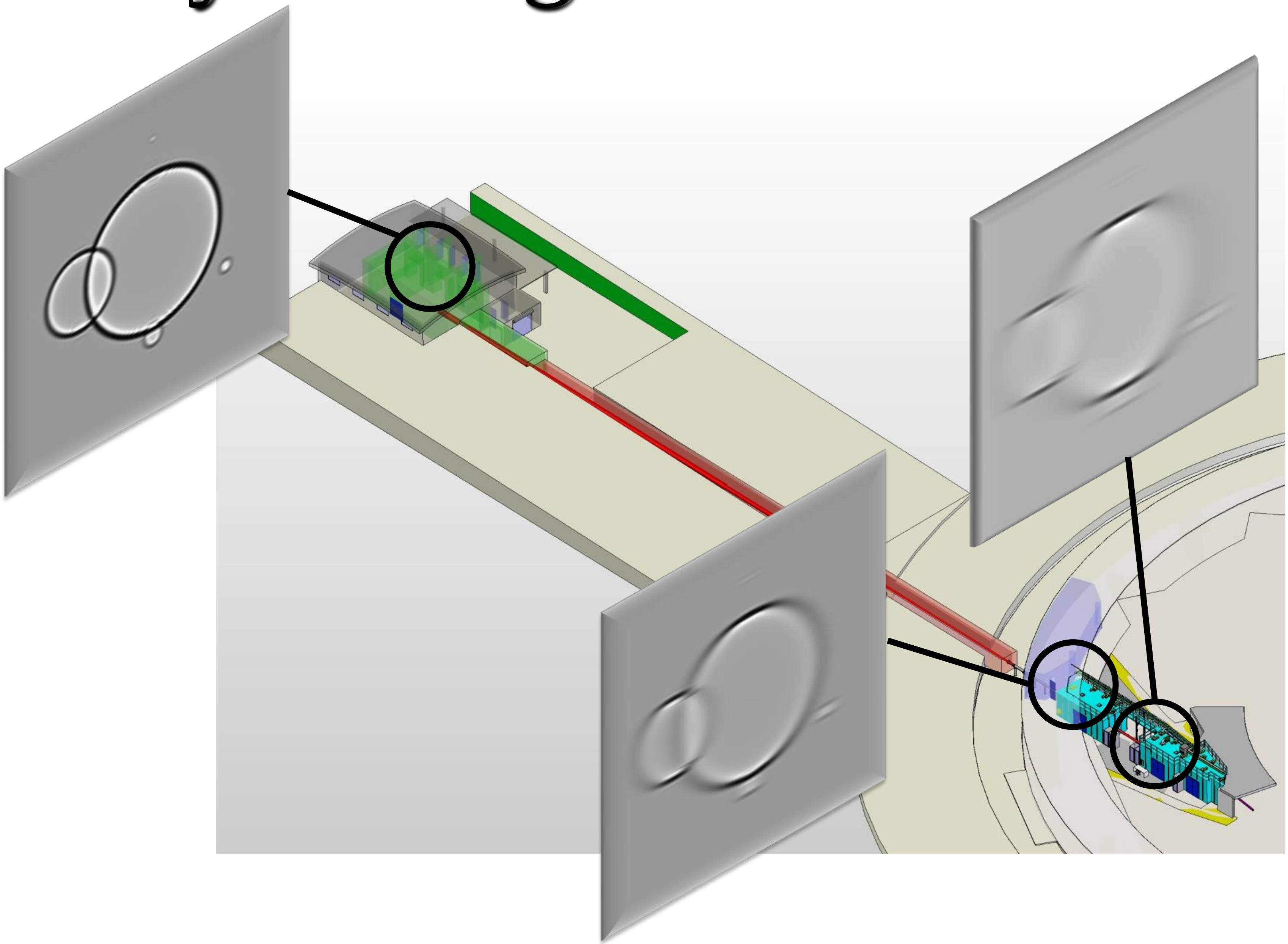
Case Study: Birth
One of the greatest Physiological challenges

- During fetal life the future airways of the lungs are liquid-filled
- At birth lungs must rapidly transform from being liquid to air filled
- How this happens is poorly understood but the process
  - Develops late in pregnancy
  - Is initiated by labour
- Preterm and caesarean section infants often develop problems
  - Incidence is increasing
  - Require weeks of assisted ventilation (>$2,000/day)
- We know that ventilating infants causes injury
  - ~30% develop chronic lung disease
  - Becomes apparent after 15 years

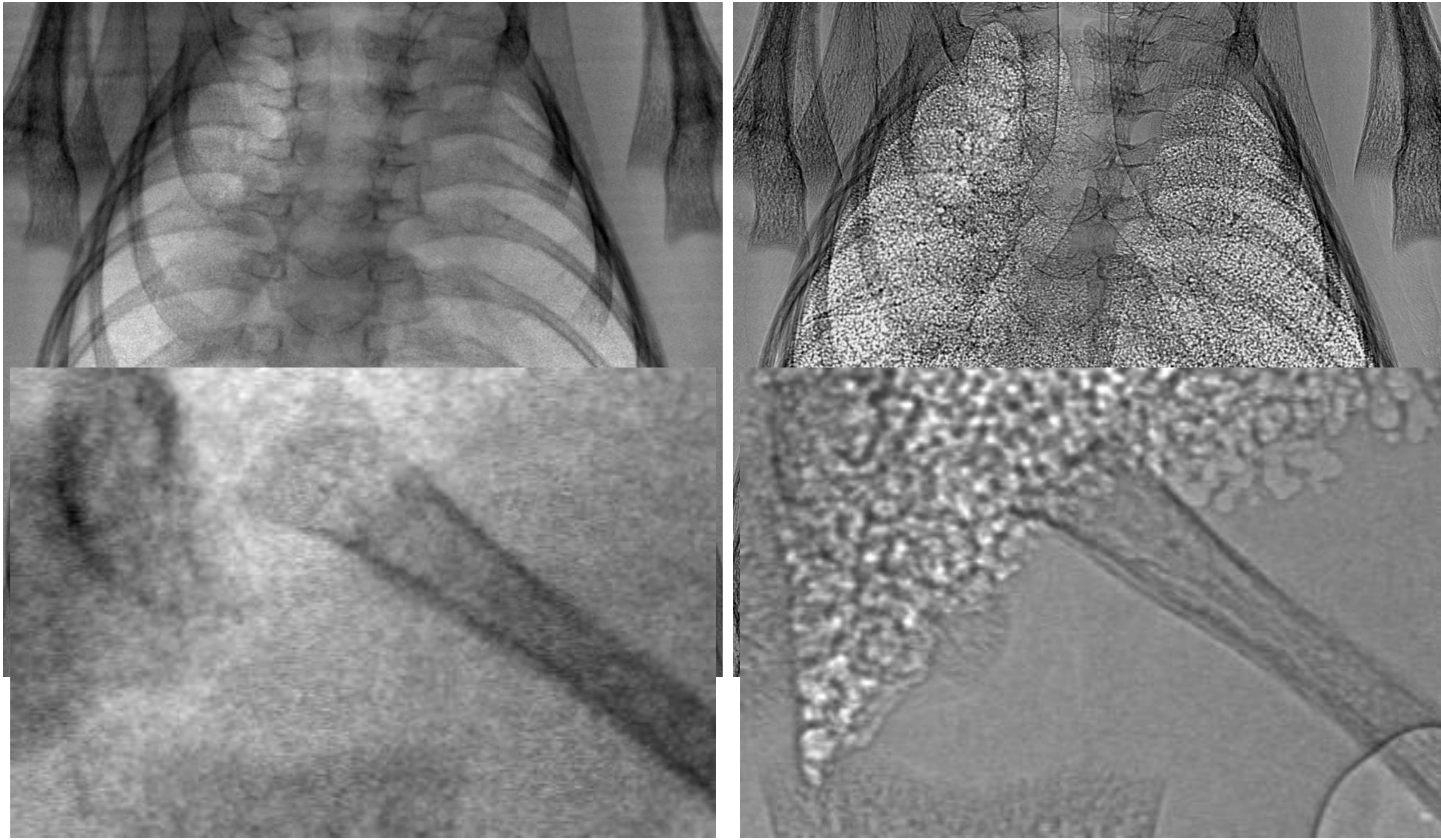
SPring-8 - Super Photon ring-8GeV

SACLA SPring-8 Angstrom **Compact** Free Electron Laser

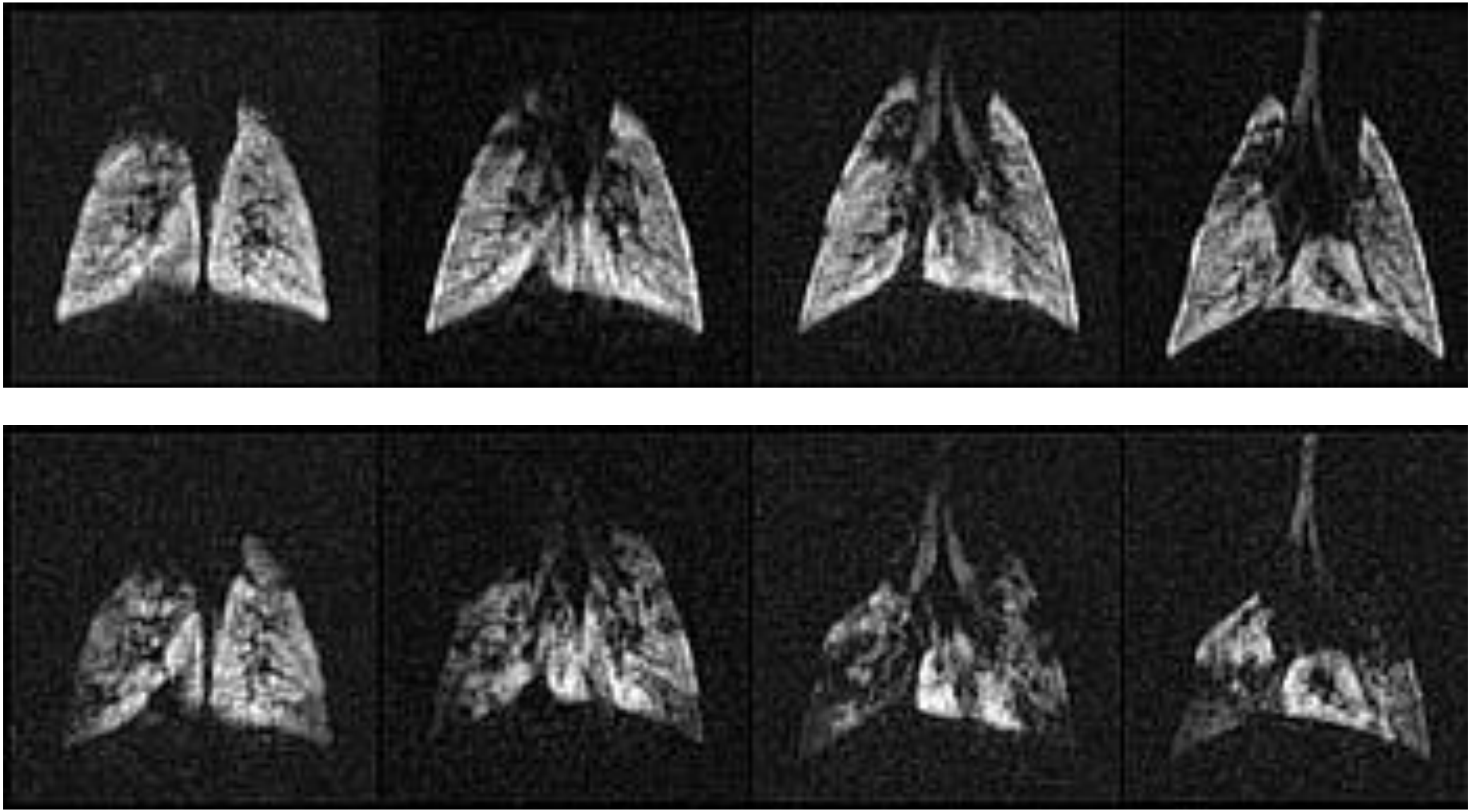
Why a Long Beamline?



Rabbit Lung



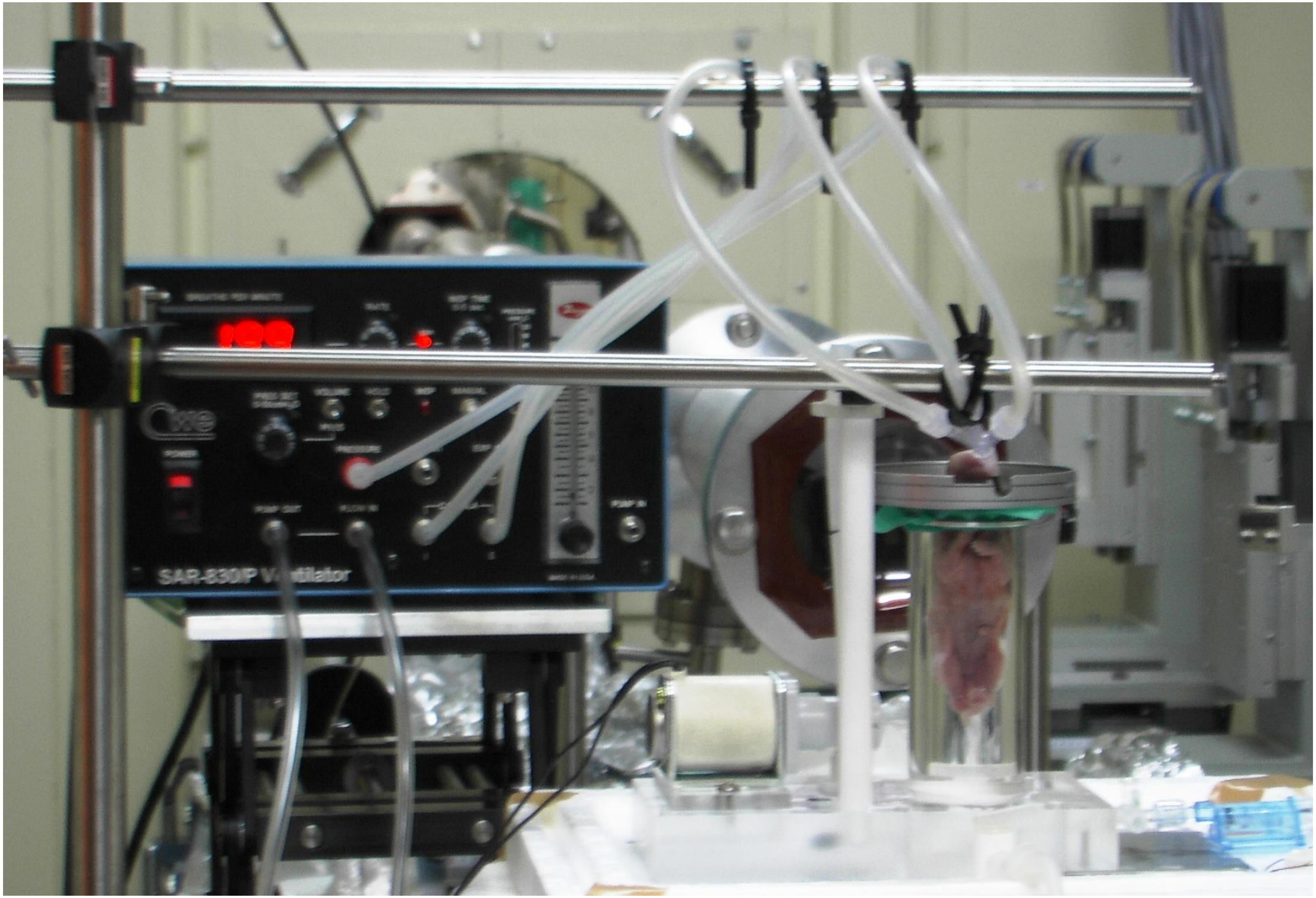
MRI State of the Art



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)

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)

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

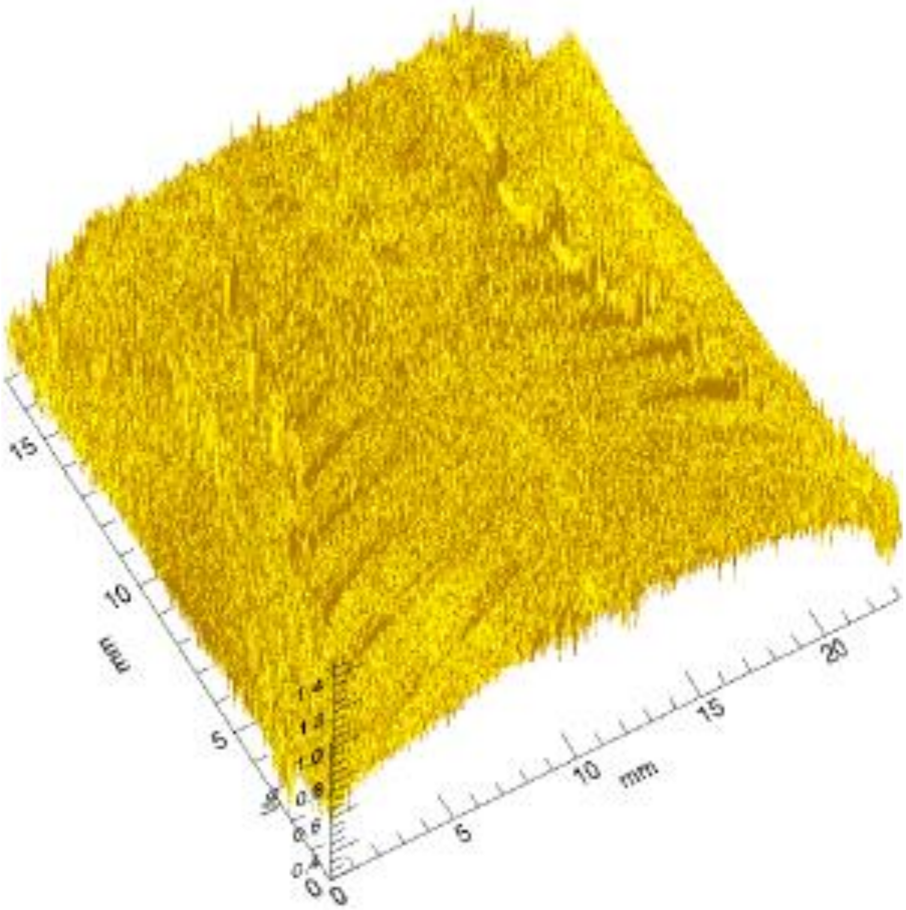
- Solve for object’s projected thickness using Fourier Derivative Theorem

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

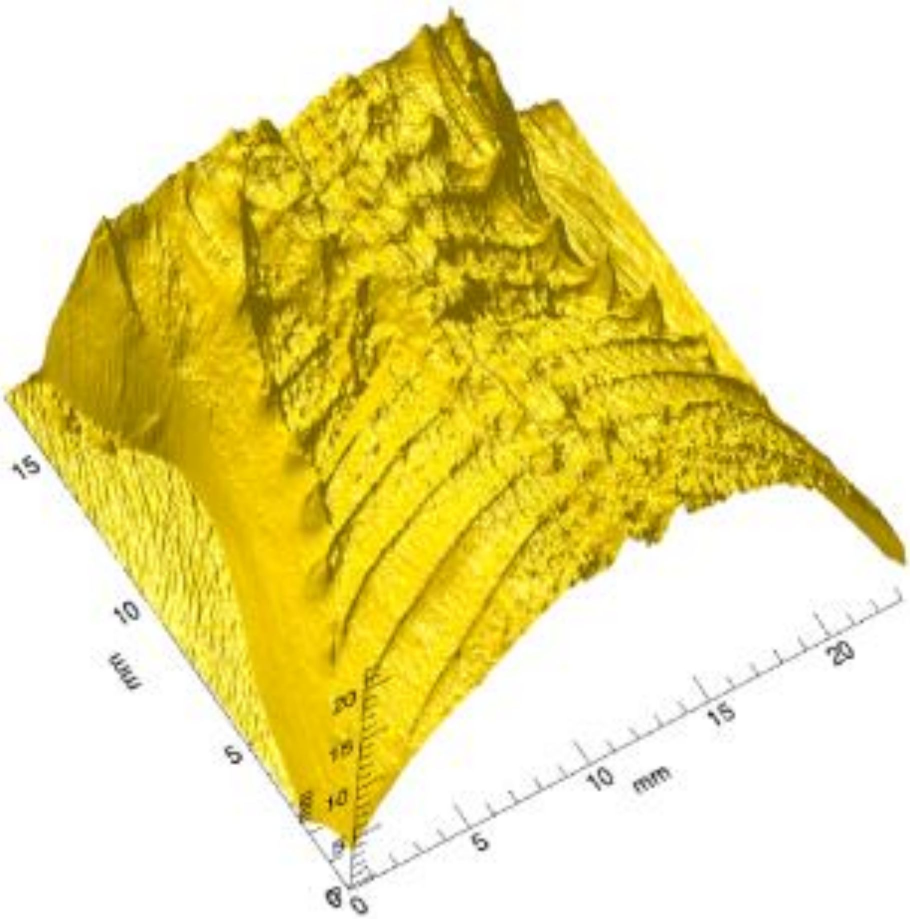
Paganin, D et al., Journal of Microscopy, Vol. 206 Pt 1 April 2002, pp. 33-40

Phase to Projected Thickness

Phase image R_2=4.26m, E=33keV



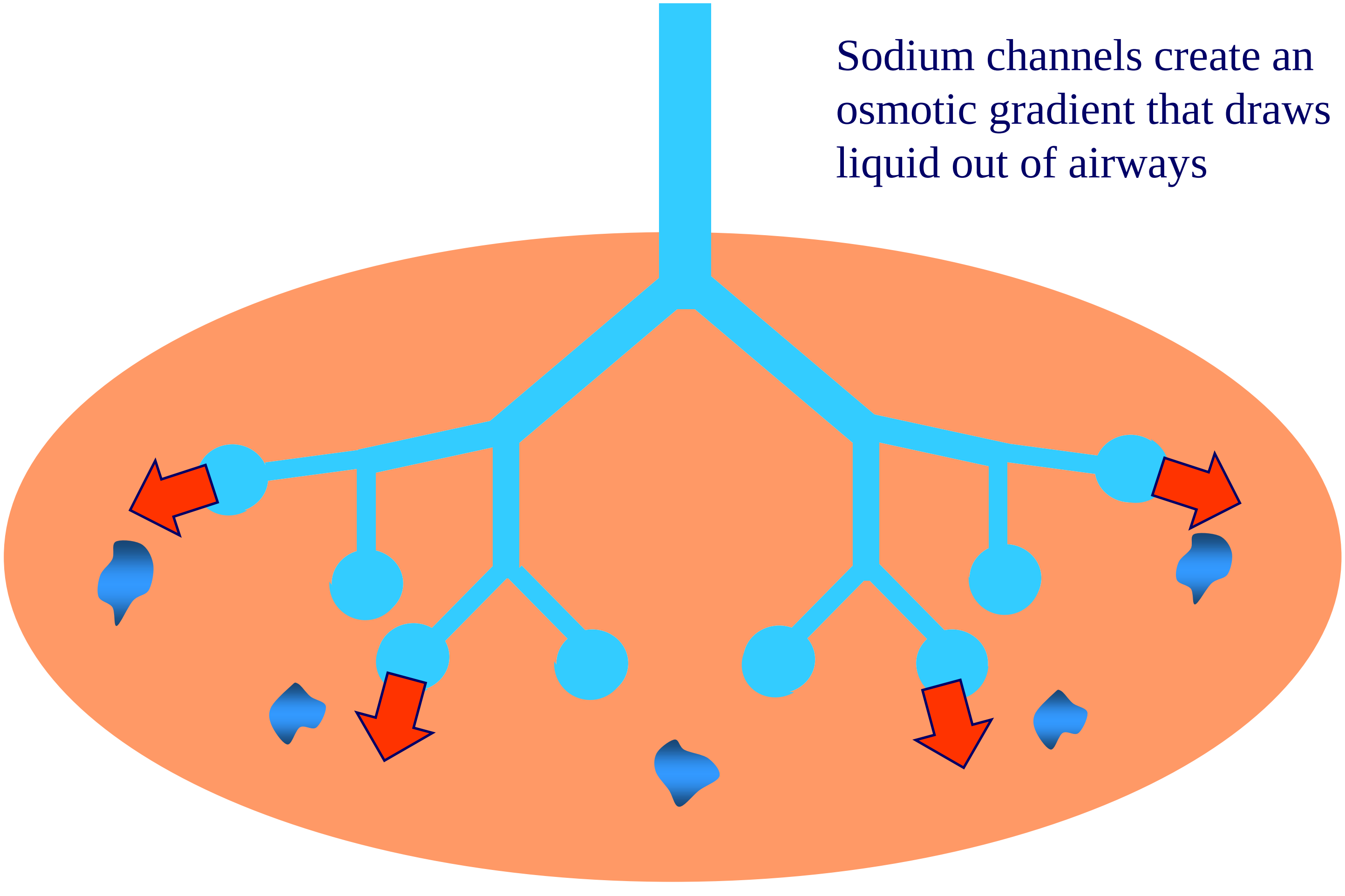
Projected thickness



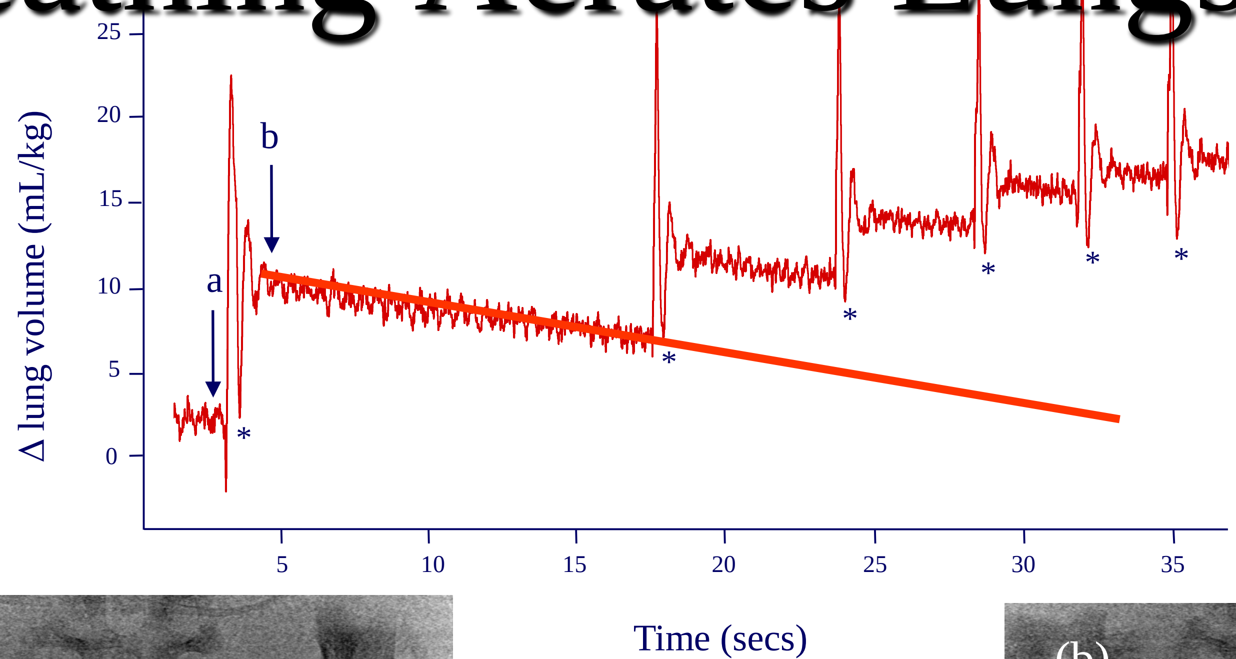
Marcus Kitchen, Monash

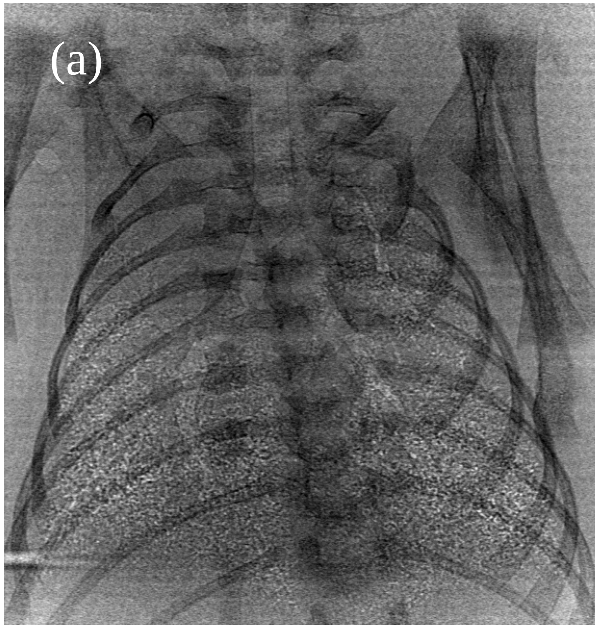
Lung aeration: Airway liquid clearance

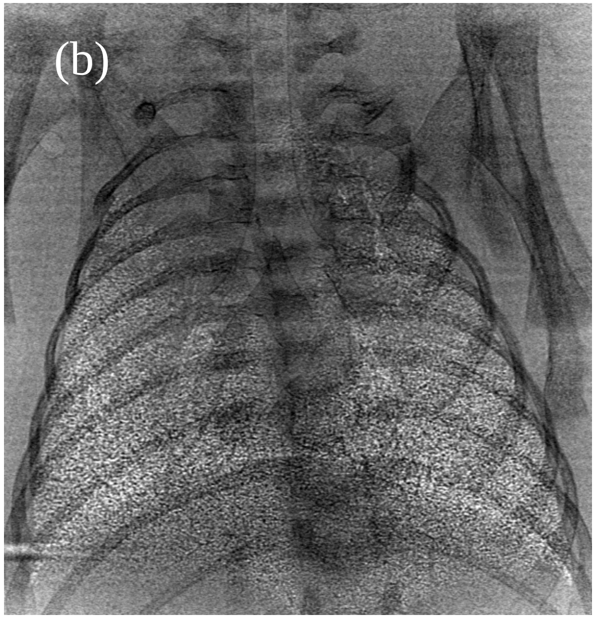
Sodium channels create an osmotic gradient that draws liquid out of airways



Breathing Aerates Lungs

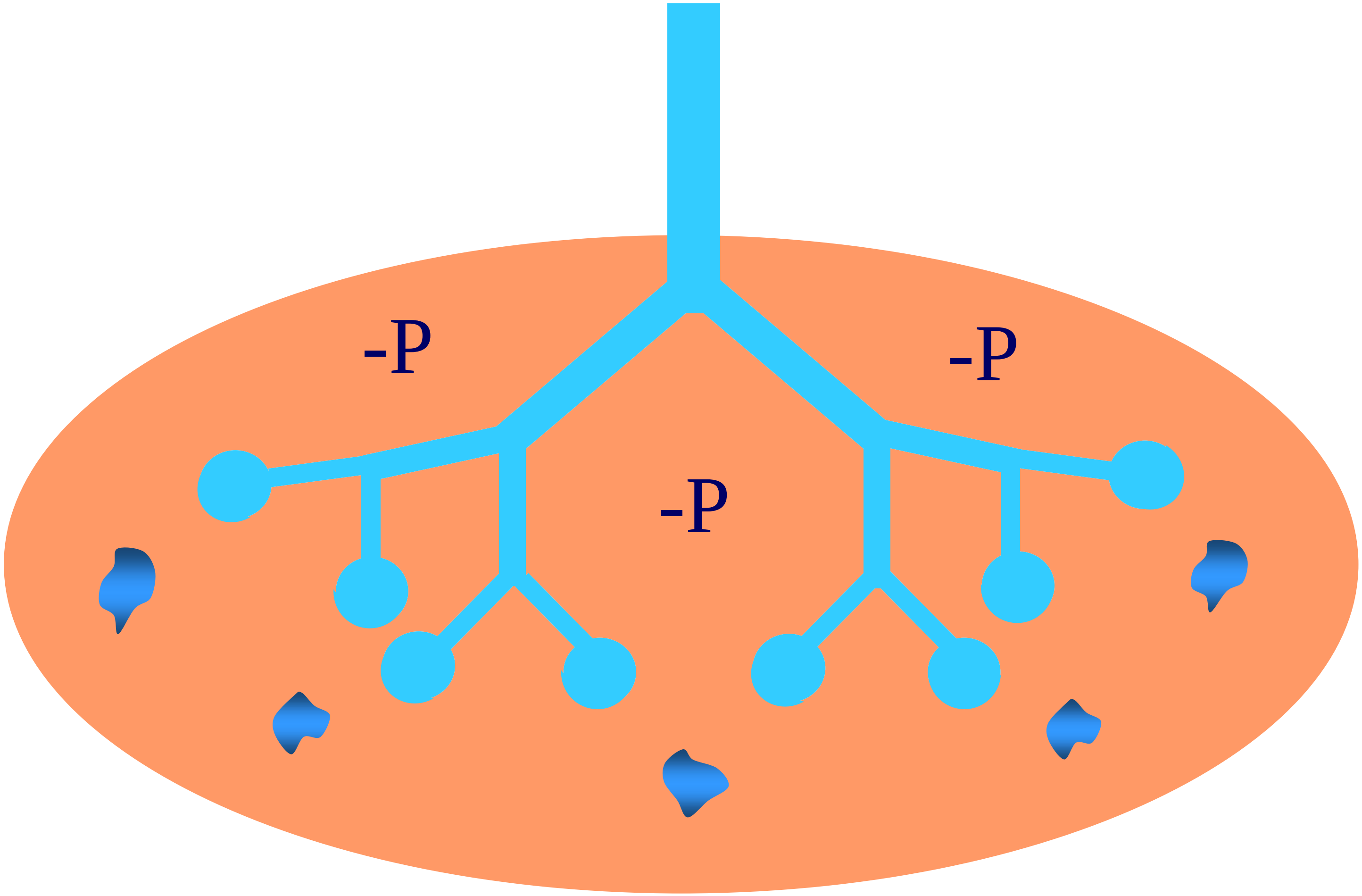






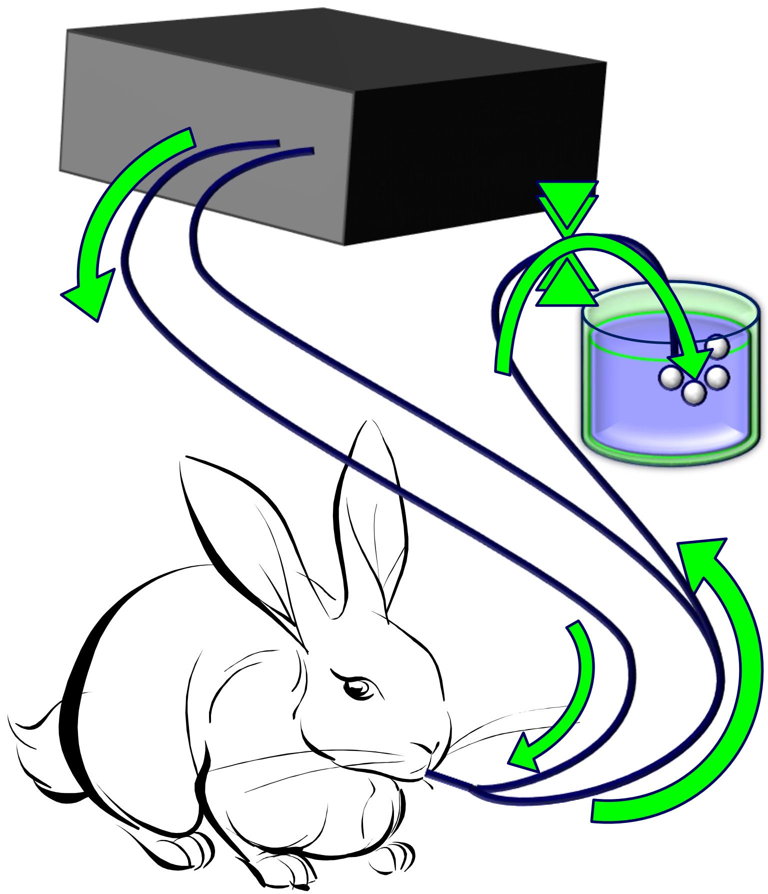
Lung aeration: Airway liquid clearance

Inspiration forces liquid out of airways

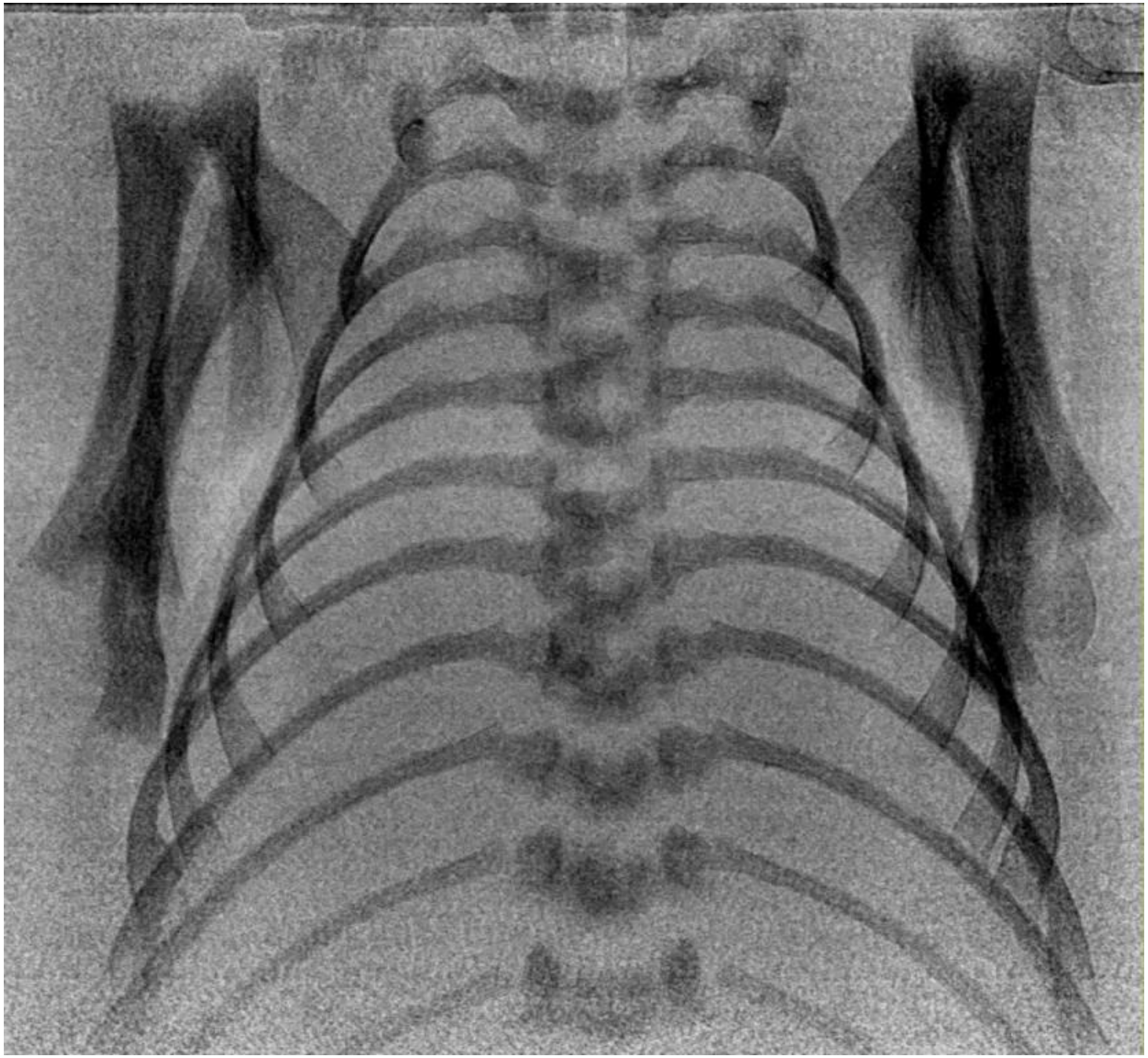


Medical Relevance

- 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

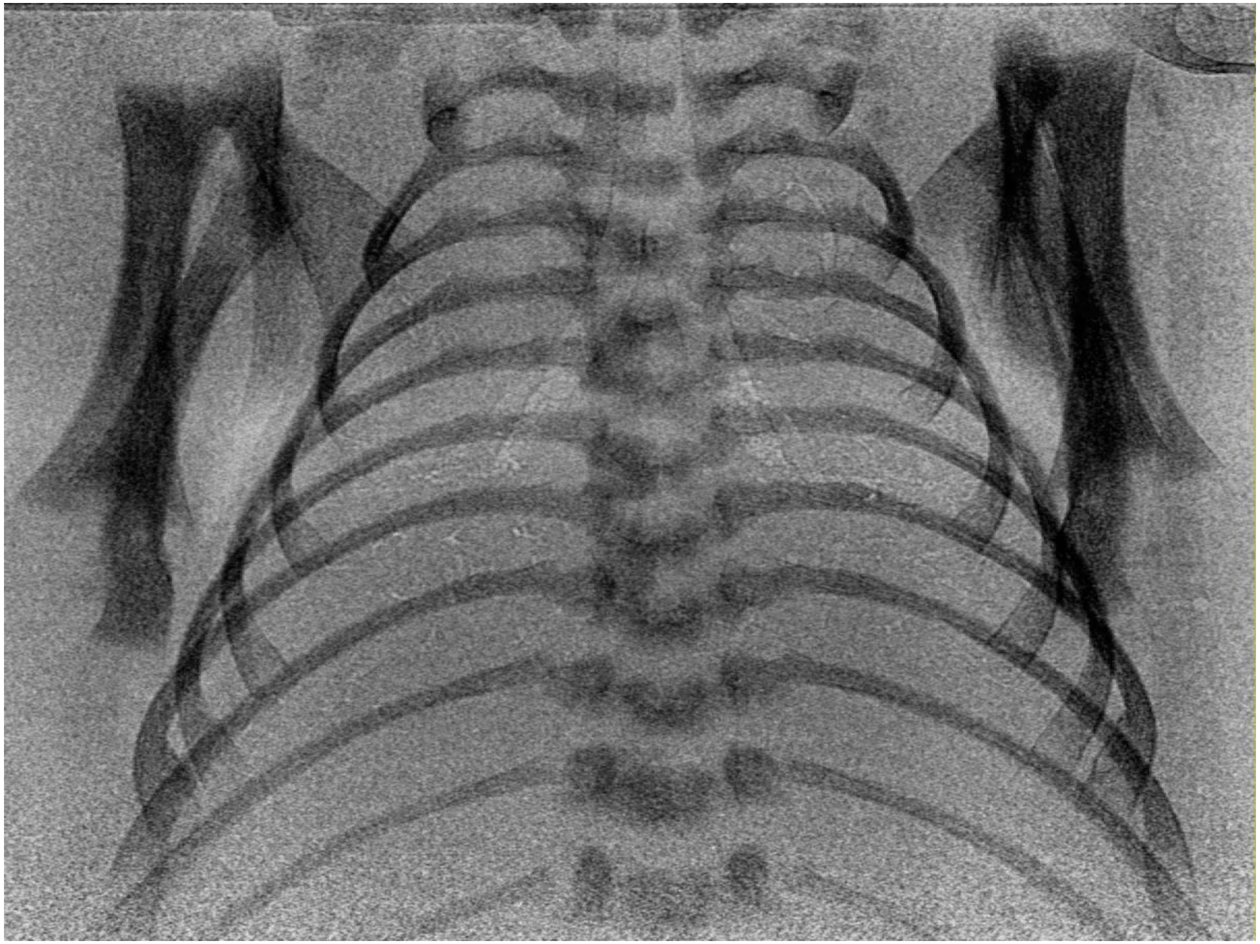


Rabbit Pup: No PEEP



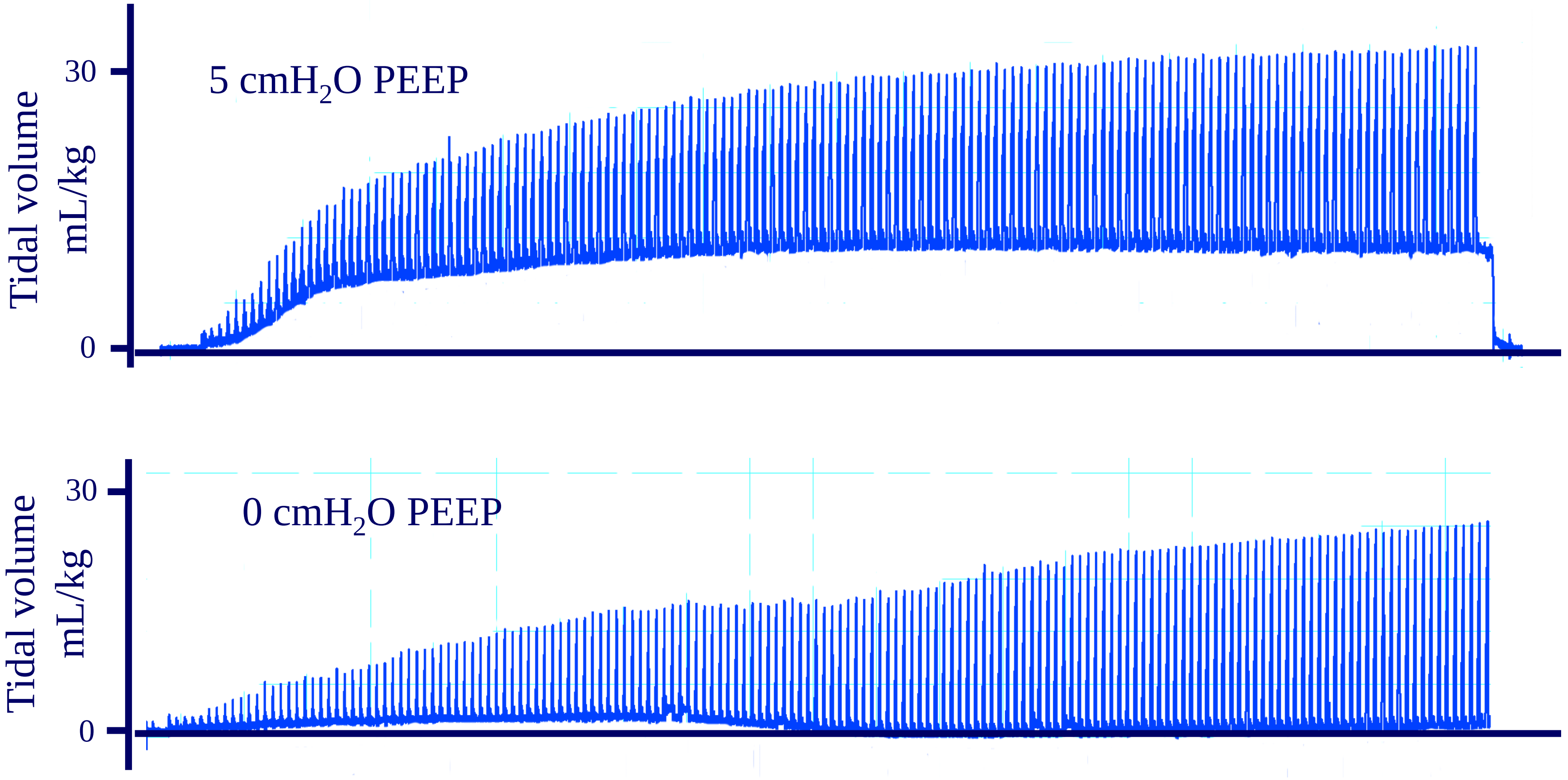
RA Lewis et al Phys. Med. Biol. **50,** 5031
S. Hooper et al FASEB **21**, 3330 (2007)

Rabbit Pup: With PEEP

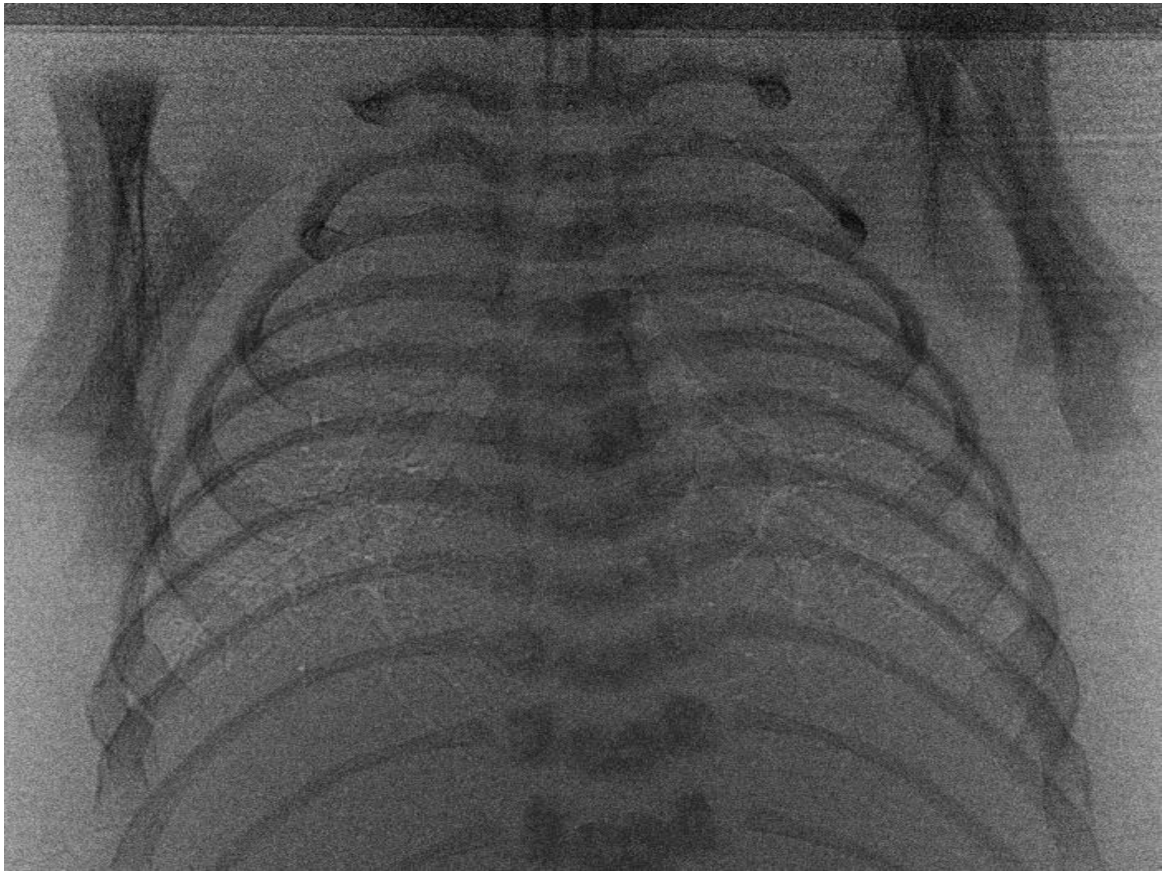


Te Pas et al Pediatric Research **65**(5), 537-541 2009
S. Hooper et al FASEB **21**, 3330 (2007)

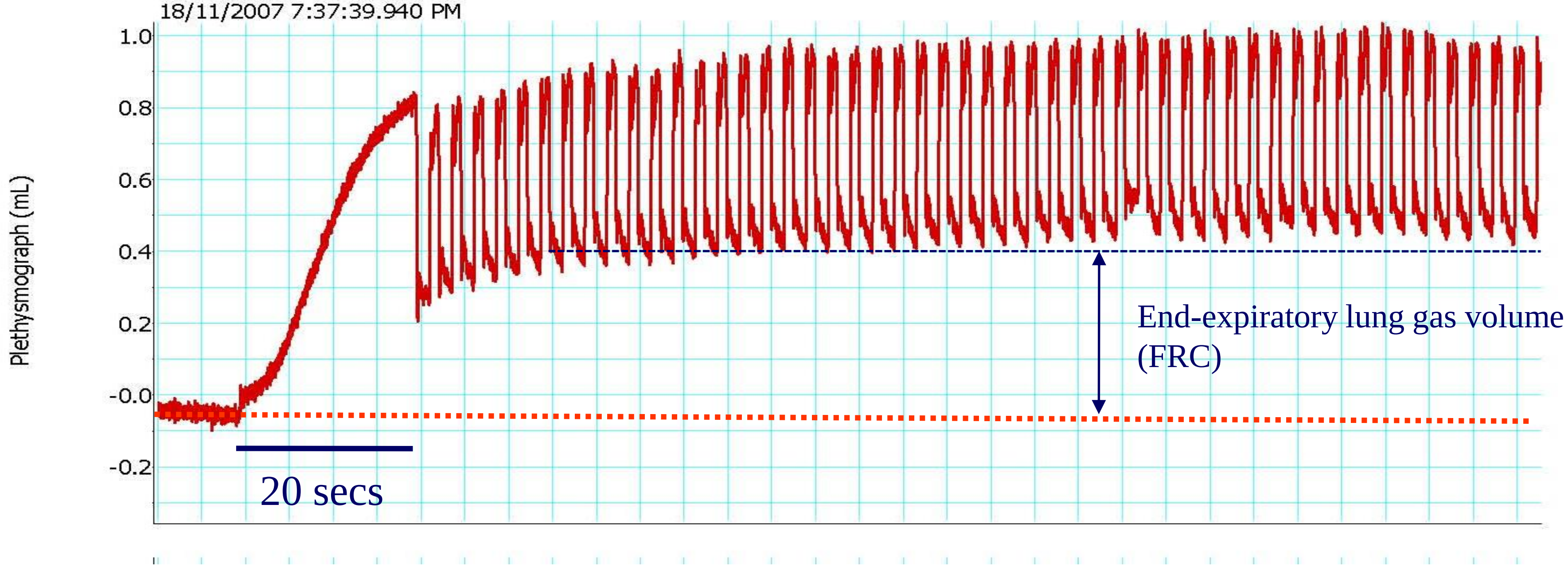
Effect of PEEP in Ventilated Preterm Rabbits



20sec First Inspiration



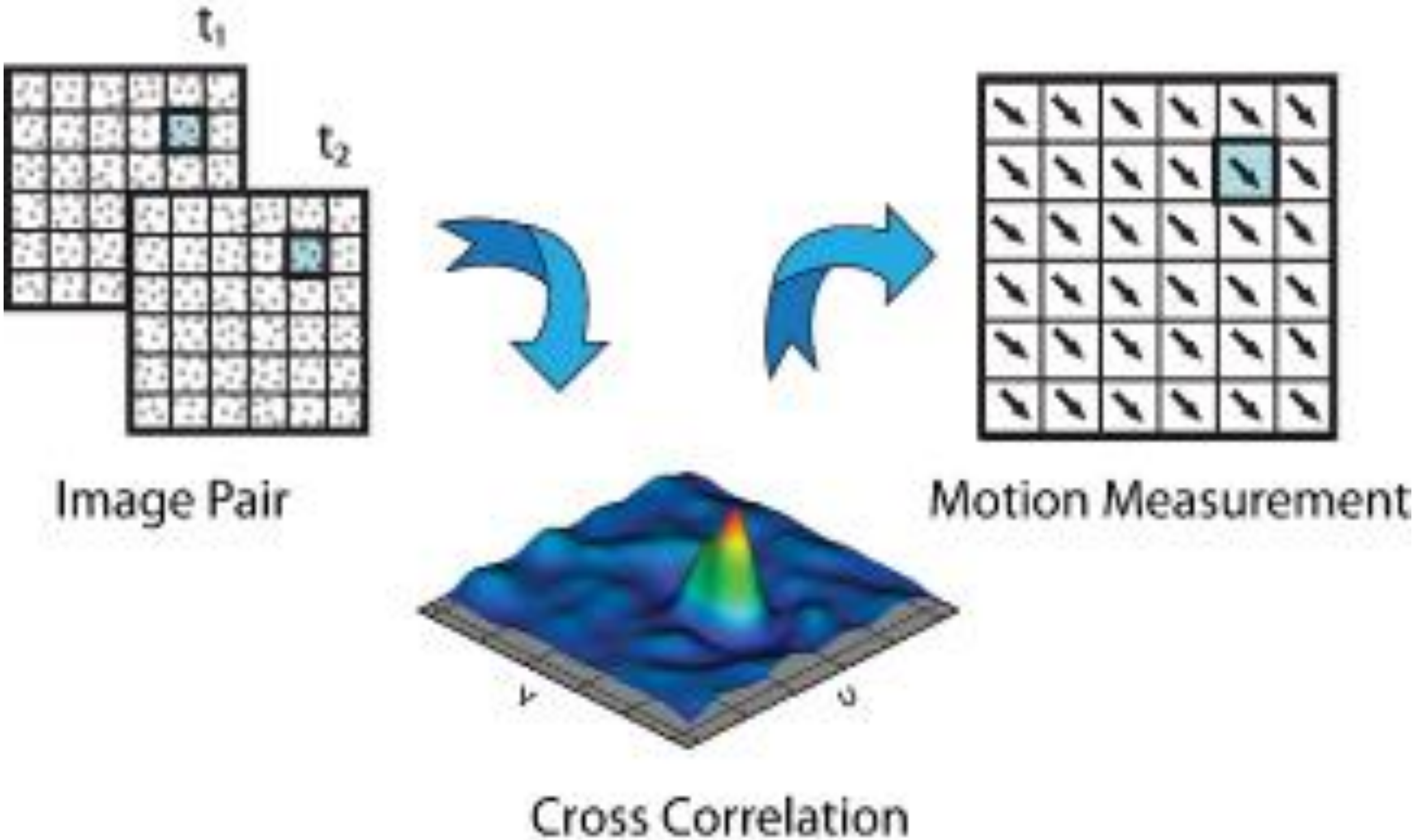
Long First Inspiration



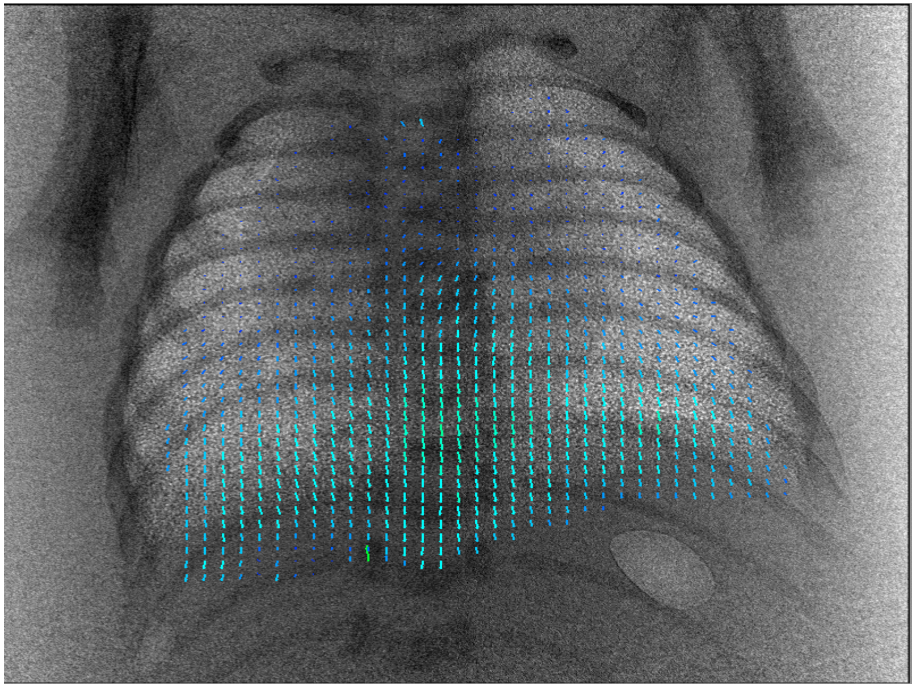
20 sec long inspiration
5 cmH_2O PEEP

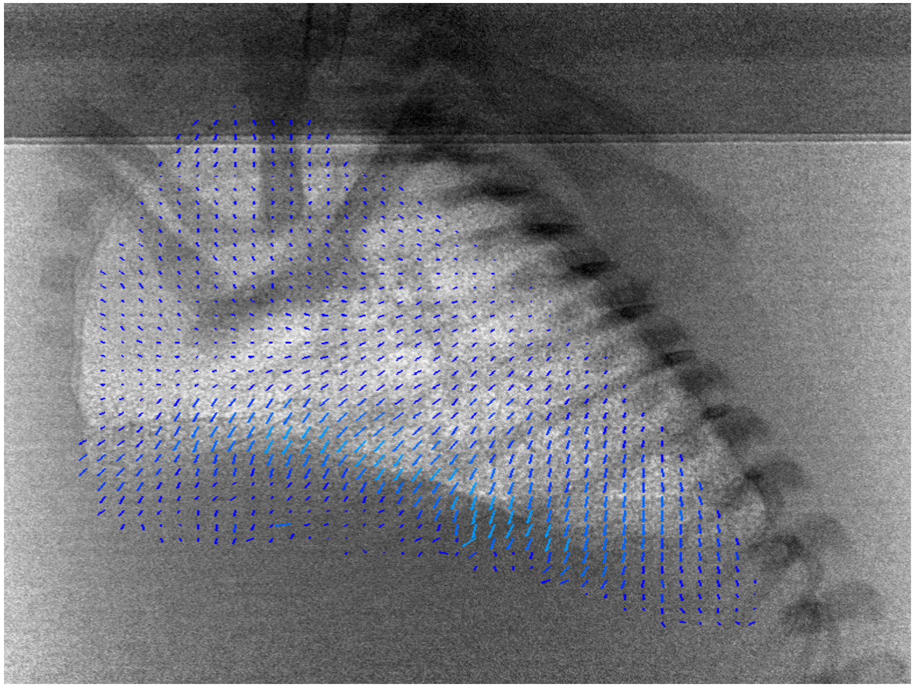
Measuring Lung Motion

- 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

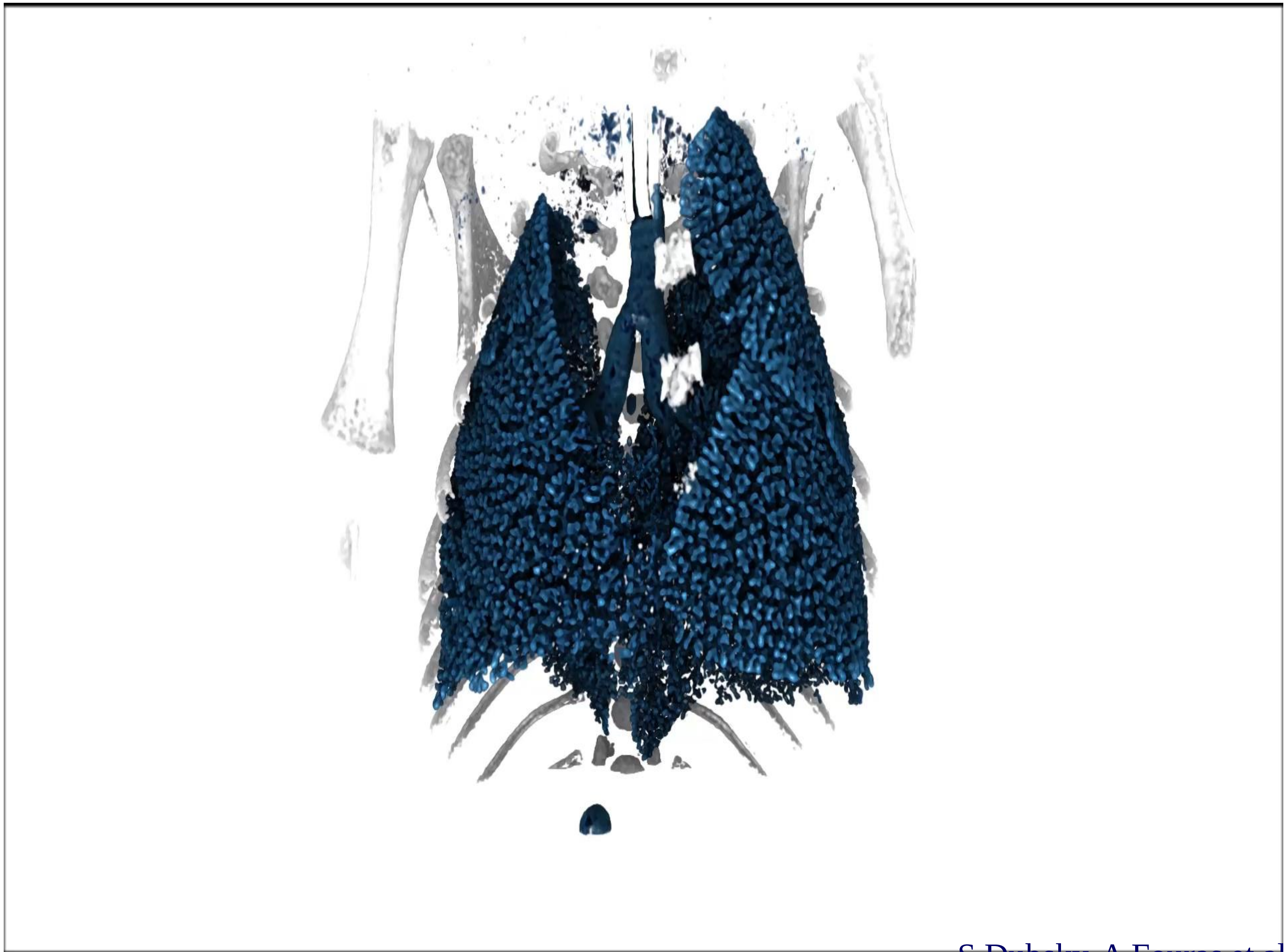
Fibrotic lung, showing regional differentiation of compliance

A. Fouras, S Dubsky et al

Moving to 4 Dimensions

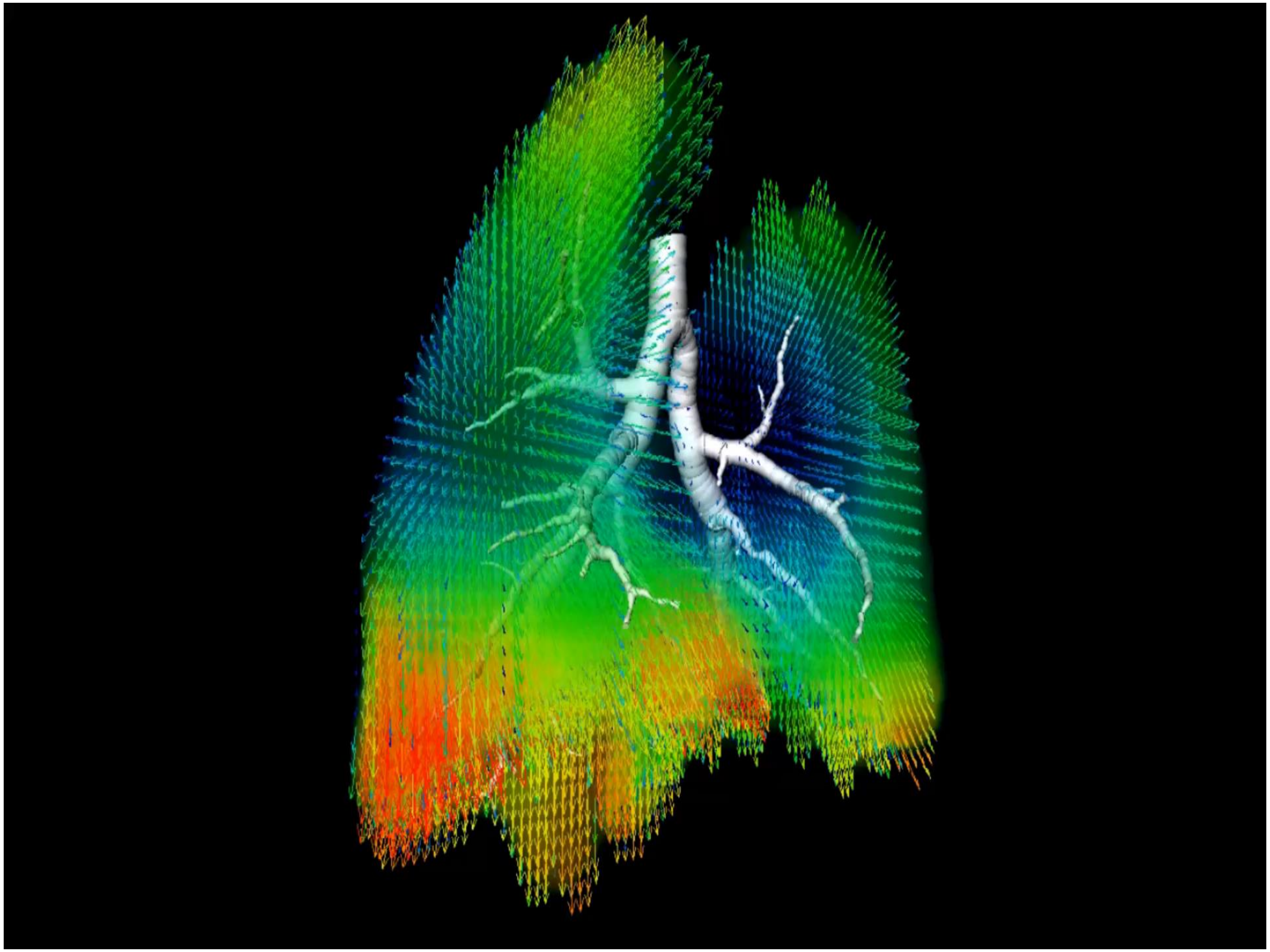
- Use controlled repeated breaths and rotate animal
- Select same point in breath for each rotation angle of animal
- Reconstruct CT image for each point in the breath

Whole Breath Lung Morphology



S Dubsky, A Fouras et al

4D PIV

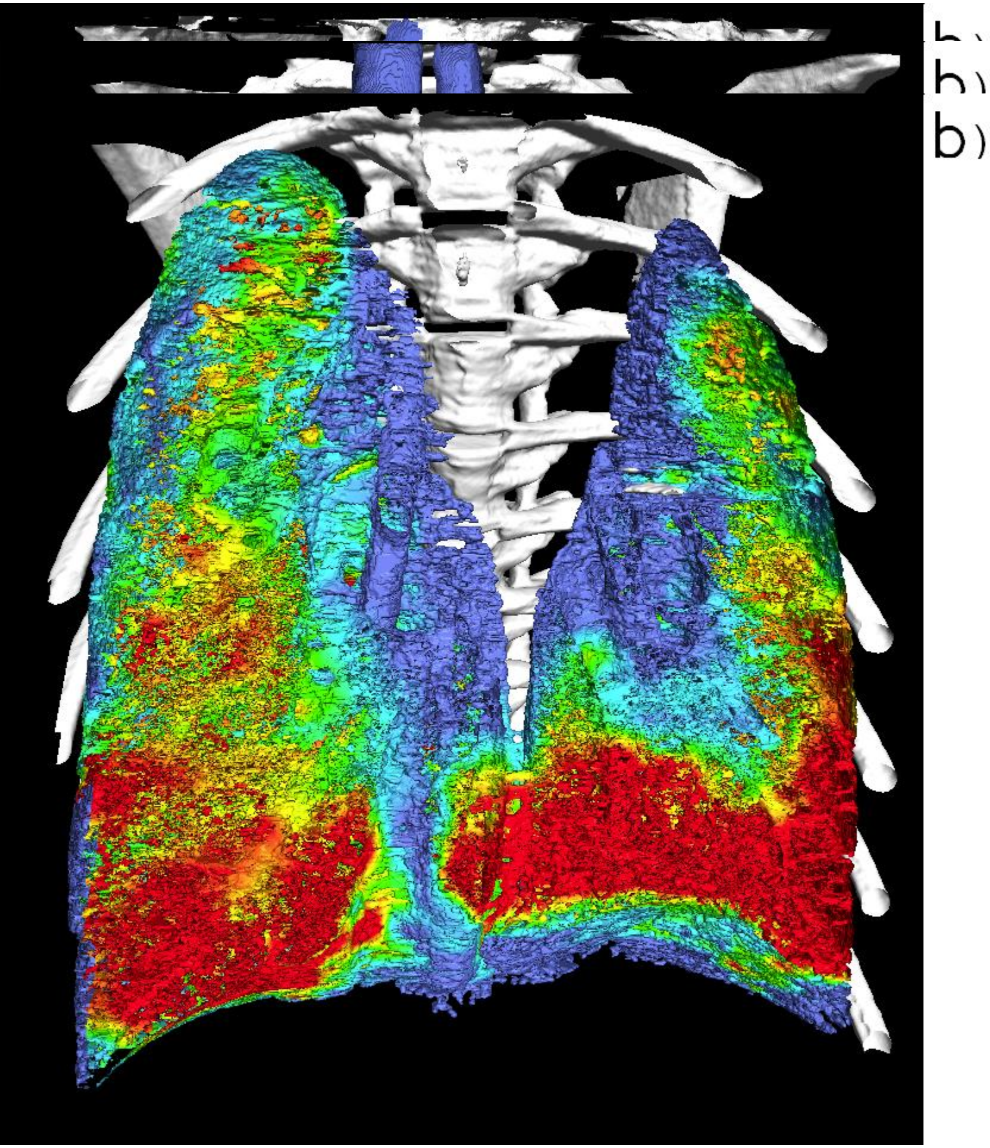


S Dubsky, A Fouras et al

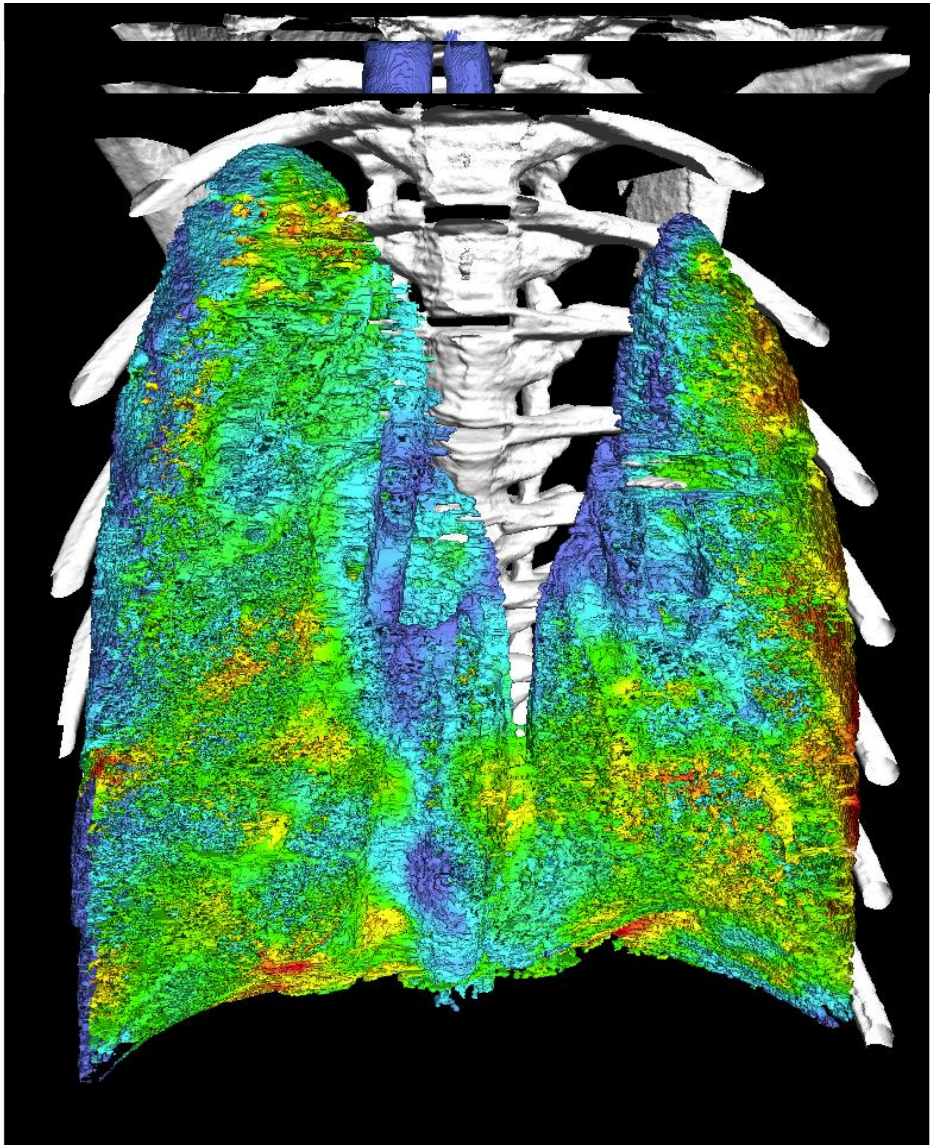
4D Flow

S Dubsky, A Fouras et al

Asthma – detecting bronchoconstriction



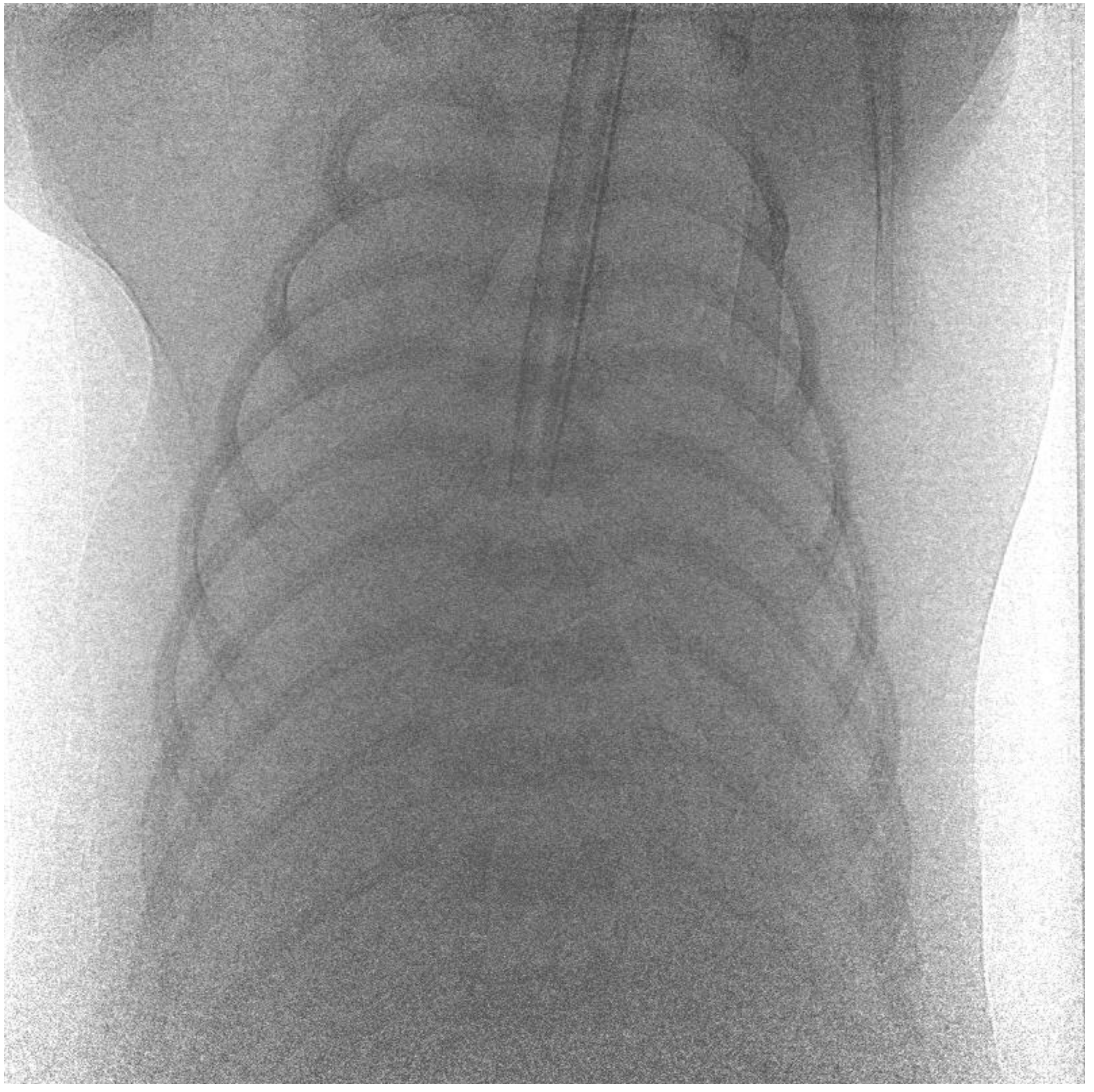
Control



Methacholine

S Dubsky, A Fouras et al

Simultaneous Phase Imaging and Angiography

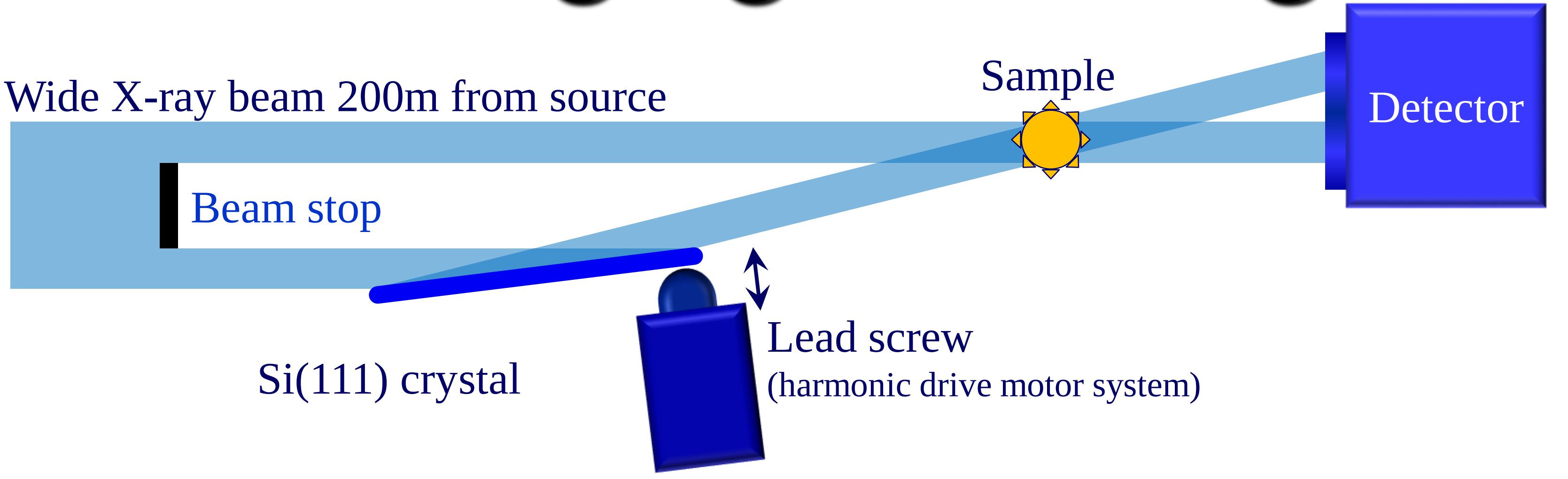


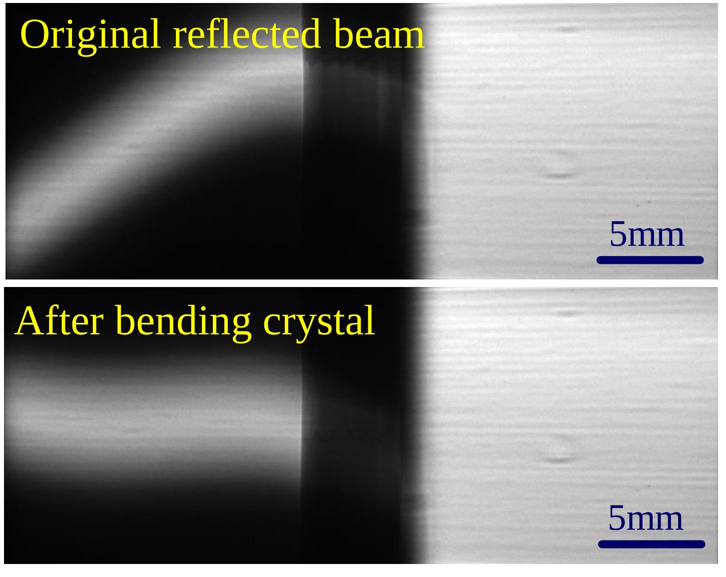
Videos used to train Doctors

Major Issues: Technical

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

Stereo imaging at SPring-8





- Distorted reflected beam a result of…
  - Vertical energy dispersion of monochromator
  - Vertical and horizontal spread of X-ray beam.
  - Deformation of first crystal in monochromator by heat load
- Corrected by
  - Bending silicon crystal by pushing one end with screw while keeping the other end fixed (see figure)

Yagi & Hoshino Spring-8

X-ray Stereo Imaging

X-ray stereo image

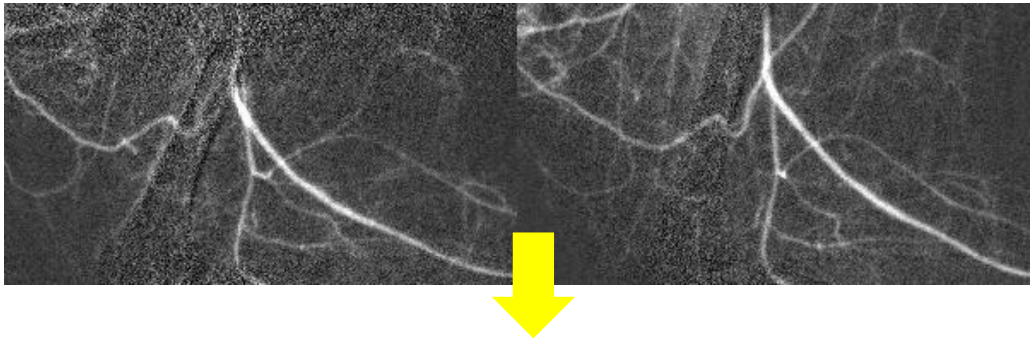
5mm

Anaglyph

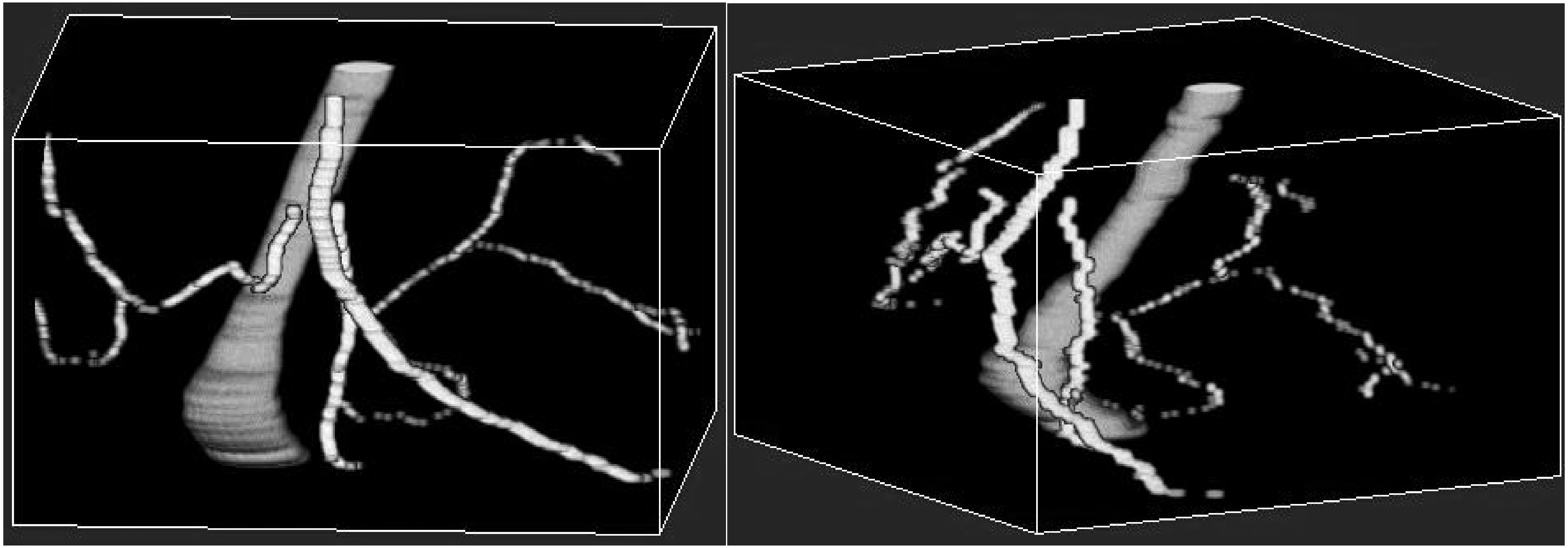
- Live Frog (*Rana japonica*)
- CCD Frame rate: 20Hz
- X-ray energy: 15keV
- Sequential images were acquired whilst vertically translating sample
- The images were combined digitally

Yagi & Hoshino Spring-8

Time-Resolved 3D Imaging



The three-dimensional arrangement of femur and blood vessels was estimated from X-ray stereo angiography.
The 3D quality is far from X-ray CT but sub-second time resolution possible



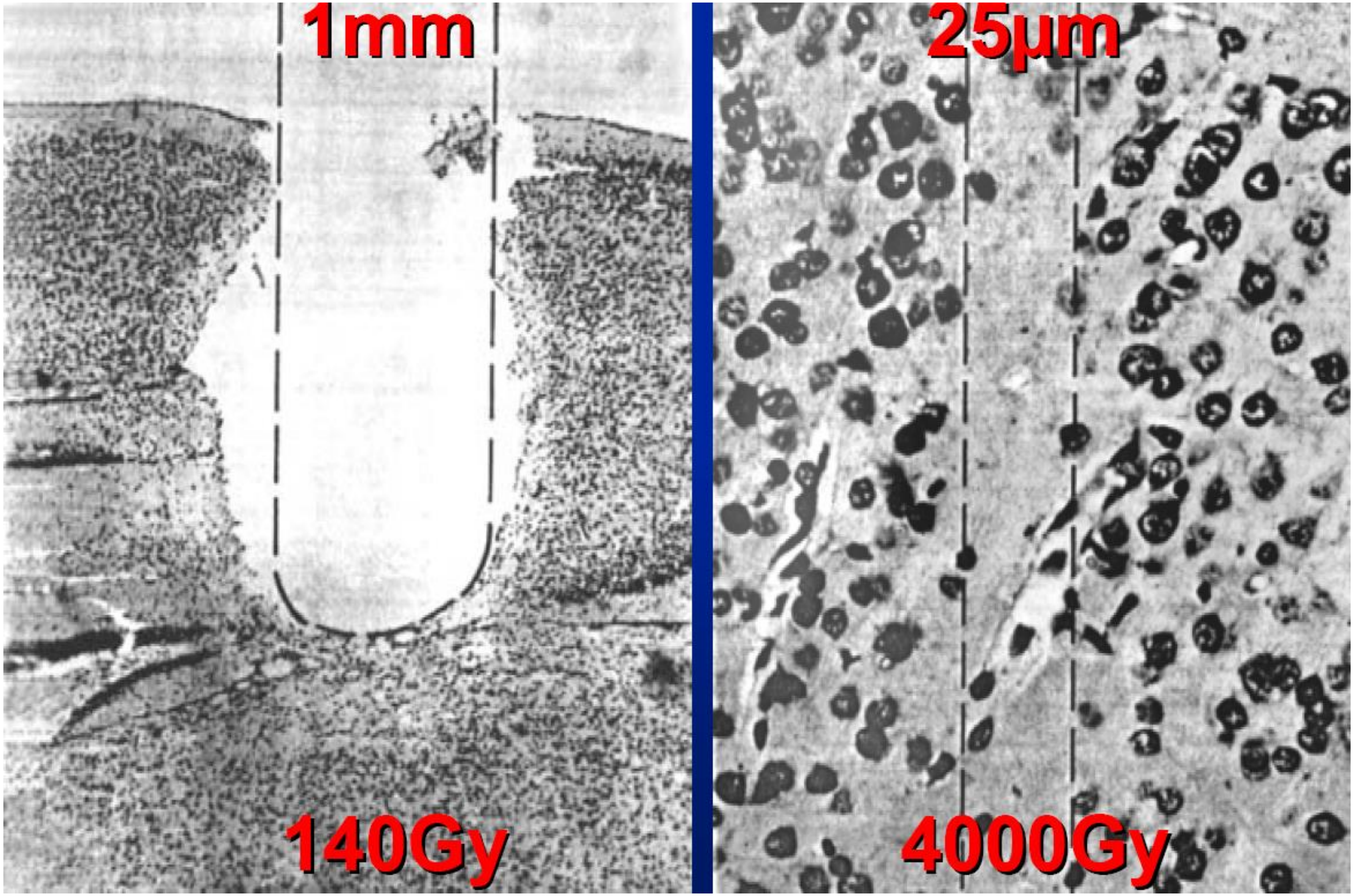
Radiotherapy

- 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

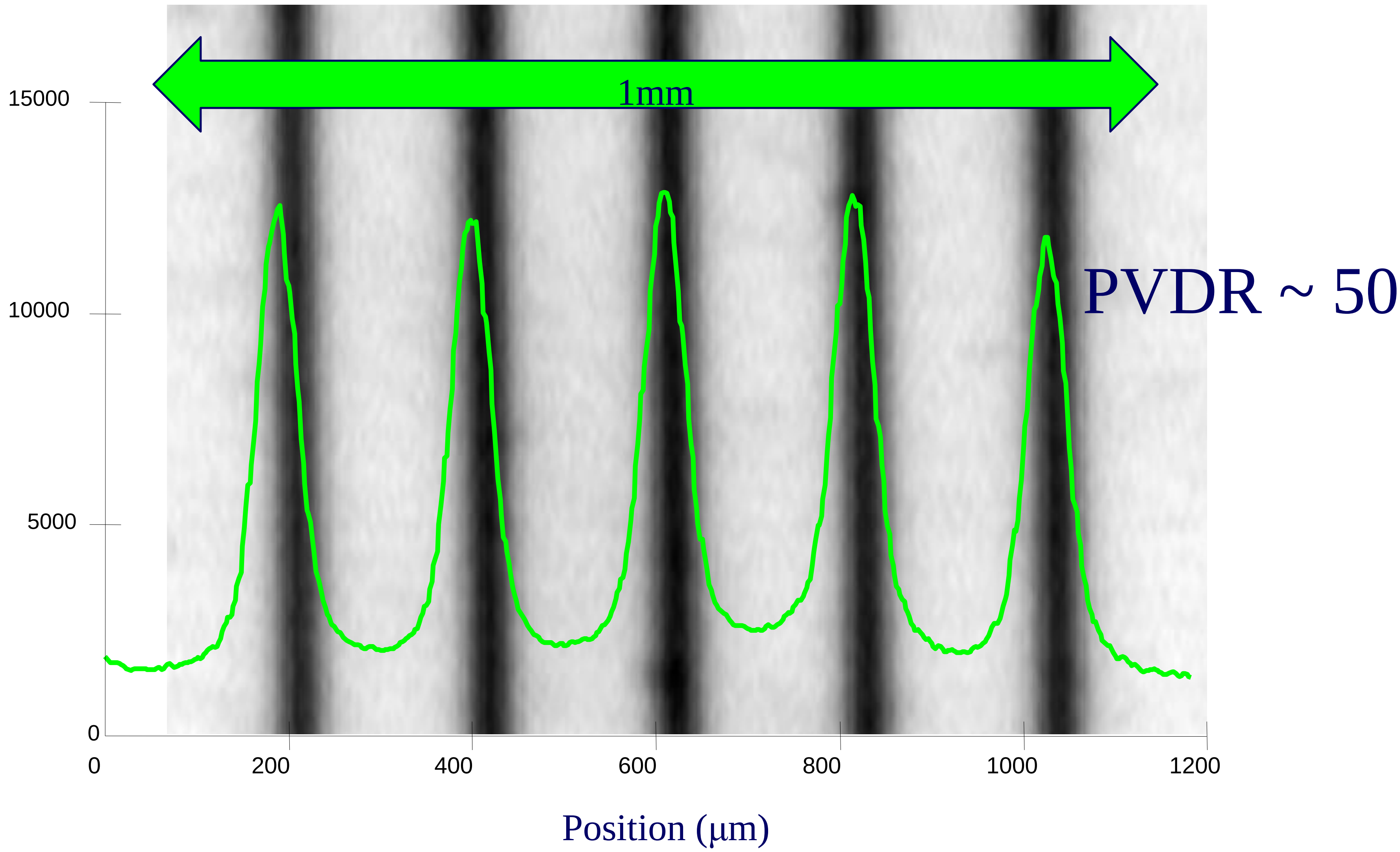
- The radiation dose that can be delivered to the tumour is limited by…..
- ..The tolerance of the surrounding healthy tissue
- Conventional Therapy
  - Uses a LINAC (high energy X-rays several MeV)
  - Uniformly irradiates tumour

Deuteron Beam: Mouse Visual Cortex

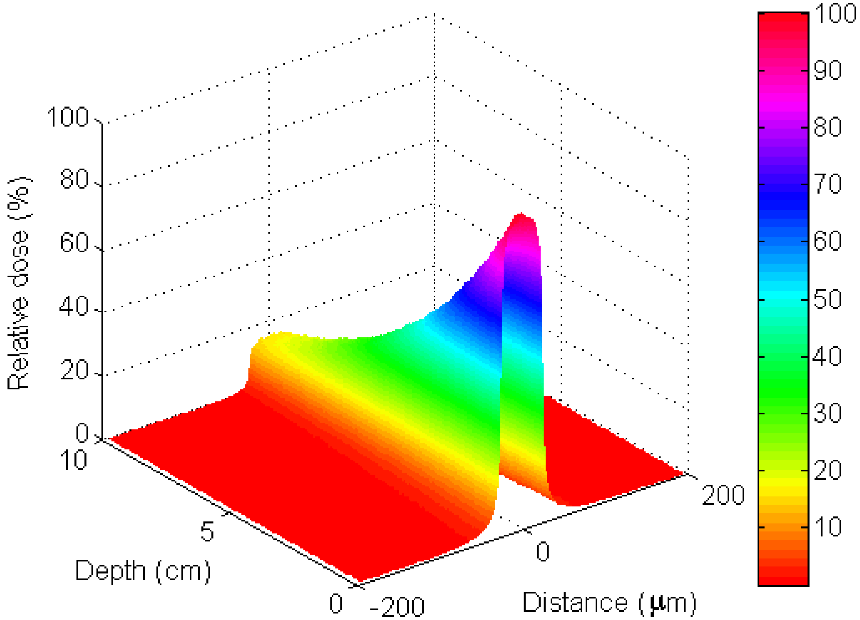


Zeman et al, Radiat Res 15 (1961) 496

Peak to Valley Ratios

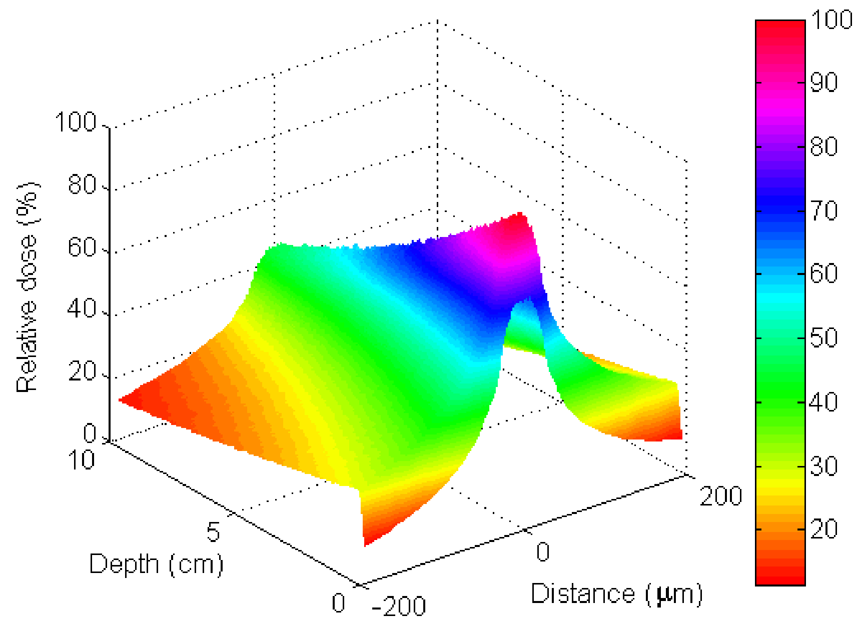


Dose Depth Curves



Synchrotron Spectrum (~100keV)

1 MeV



A Bravin

Loss of Pattern with Depth

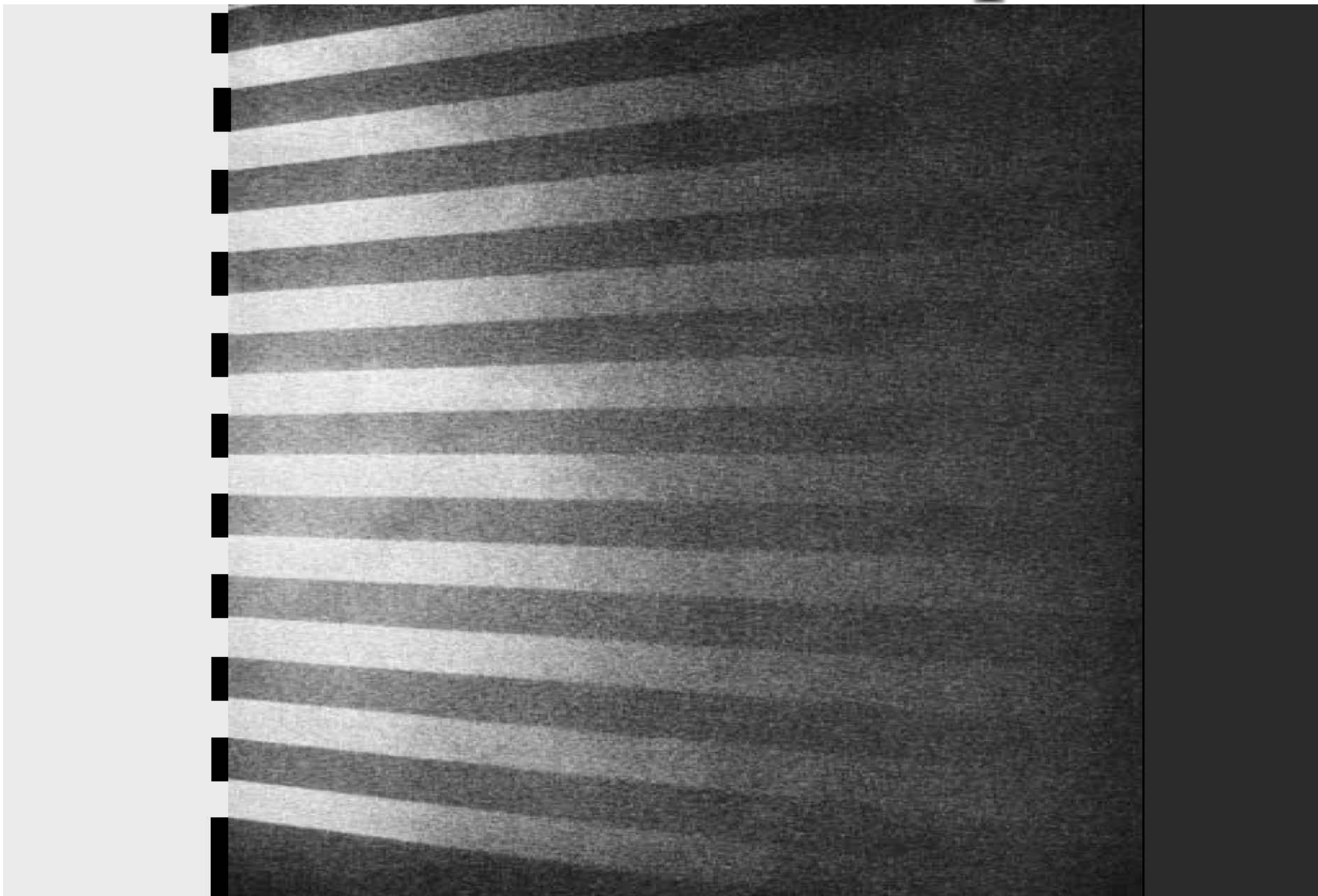
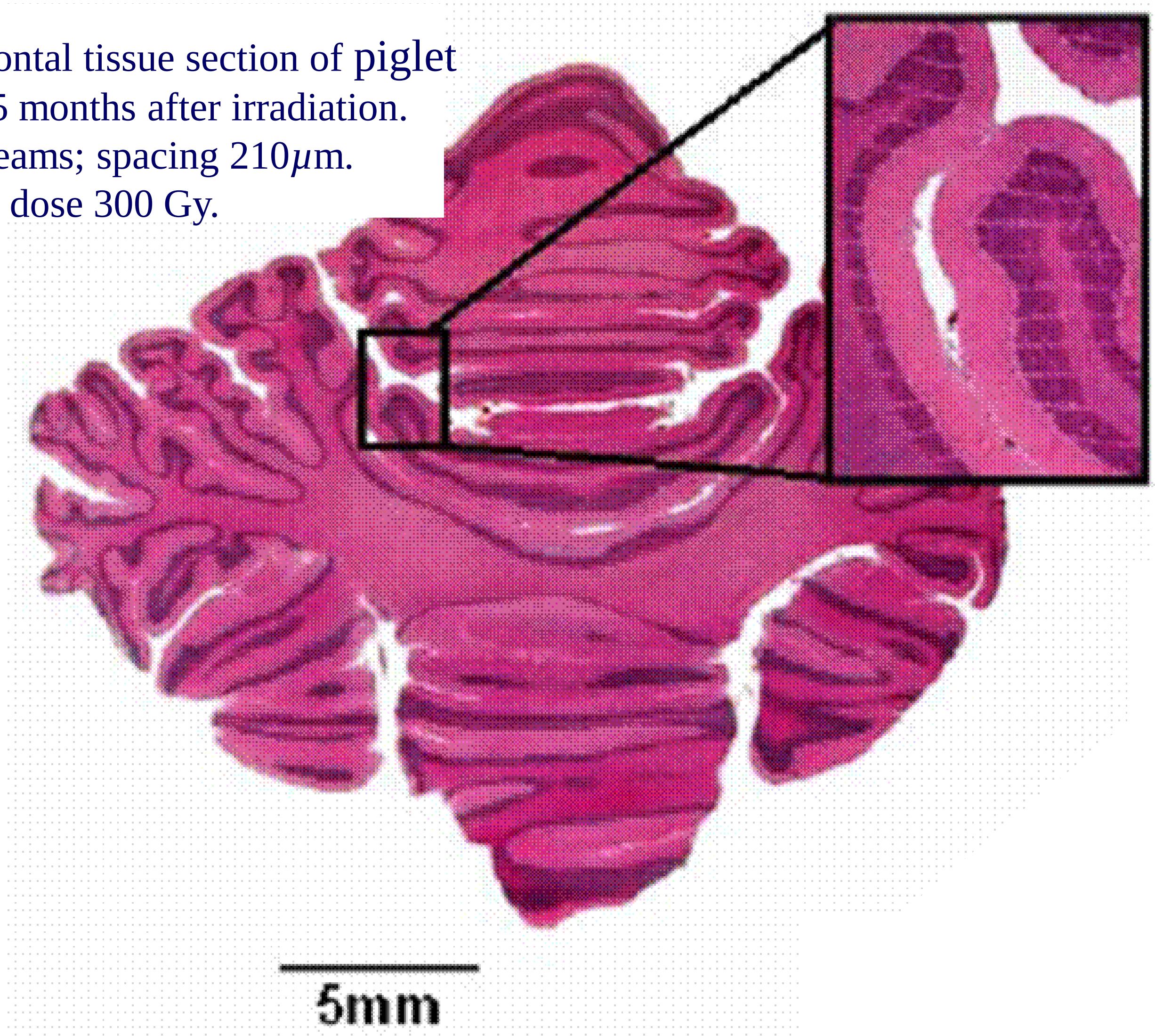


Fig. 43. Shafts of radiation through sieve fields showing divergence and obliteration of sieve pattern in depth

Jolles, 1953

Piglets

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

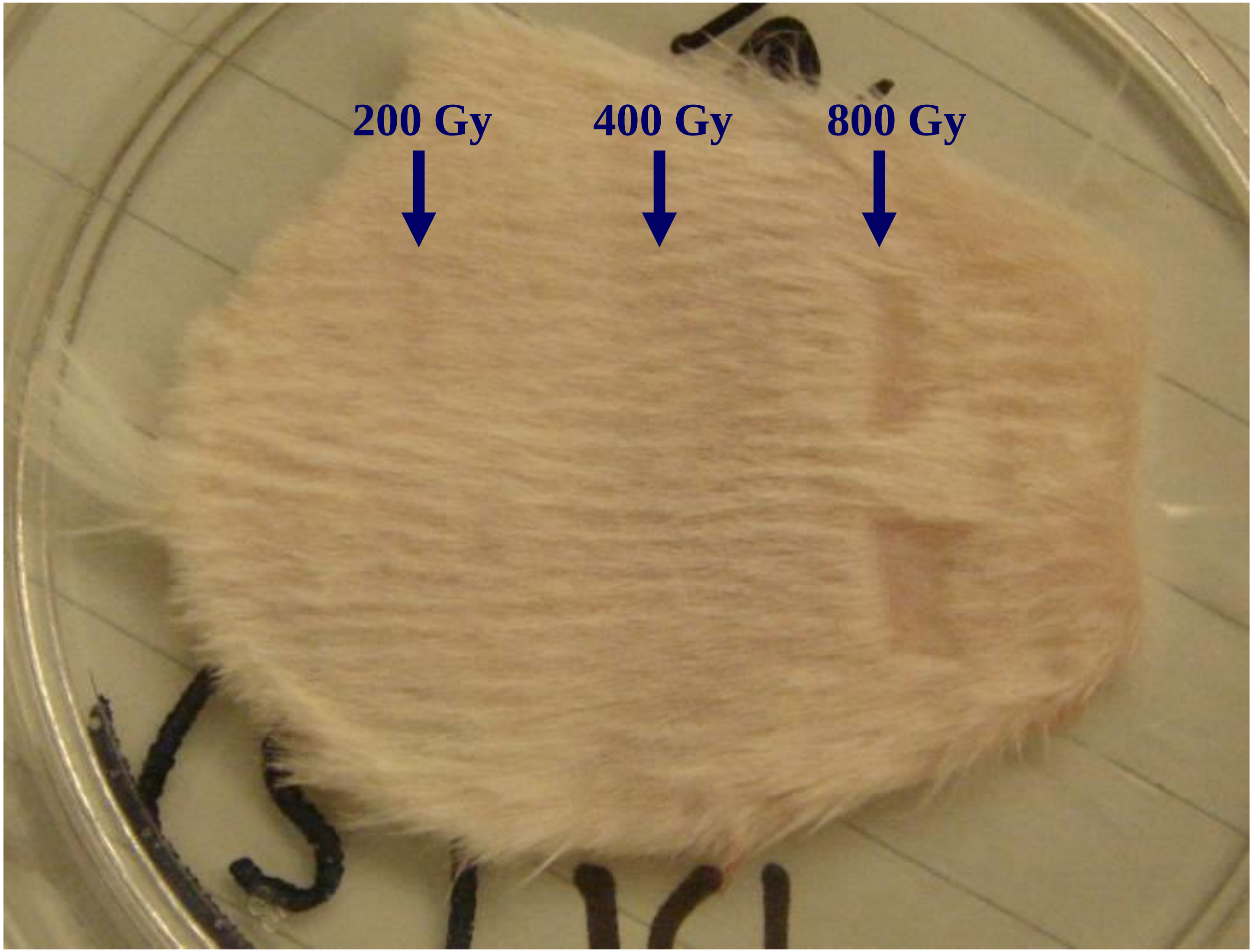


Laissue J A *et al* 2001 *Proc. SPIE* **4508** 65–73

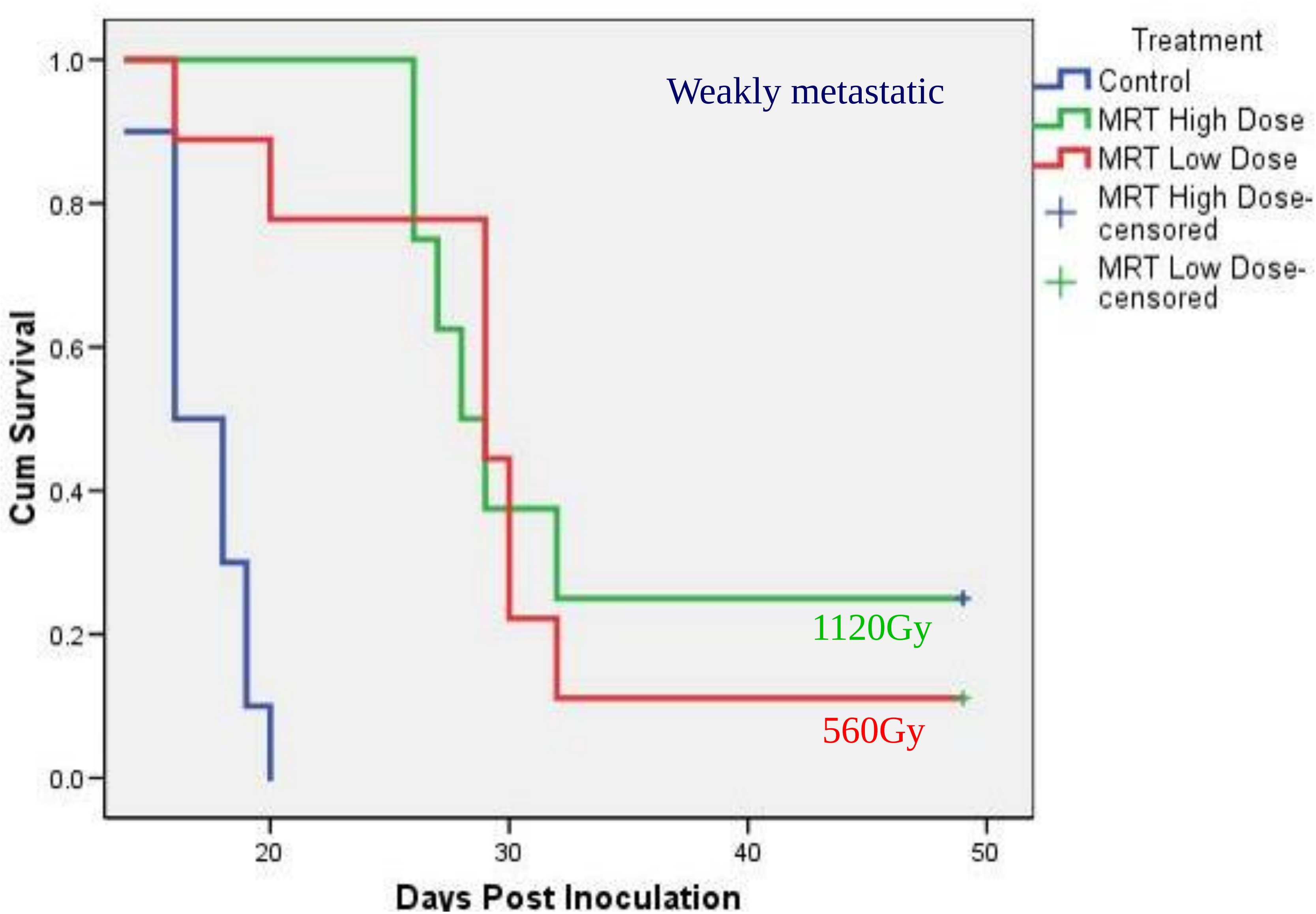
MRT on Mice

- 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

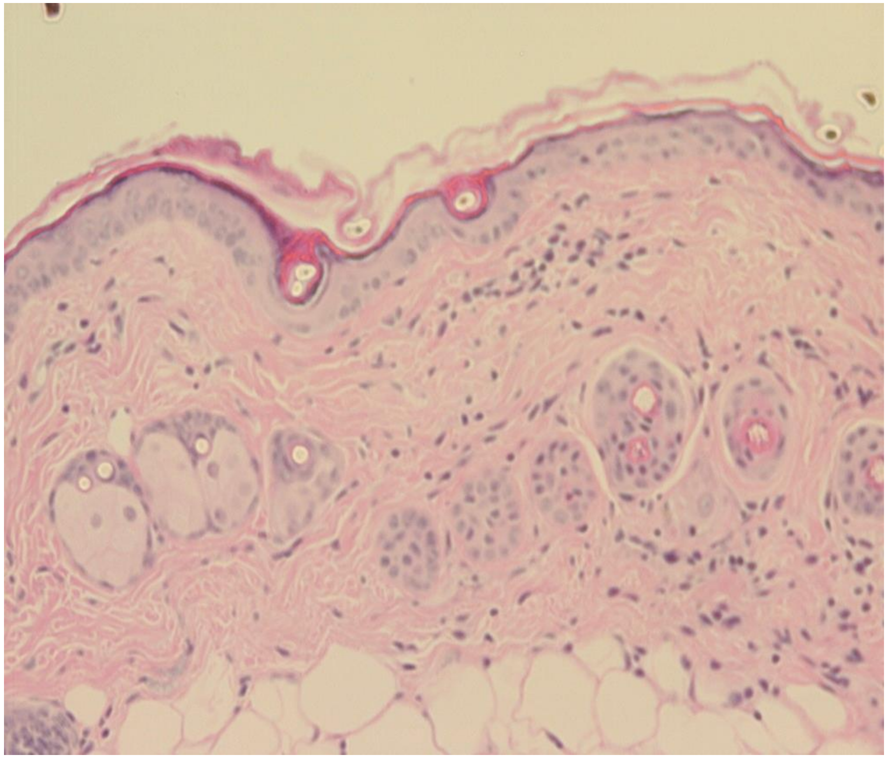
Exfoliation

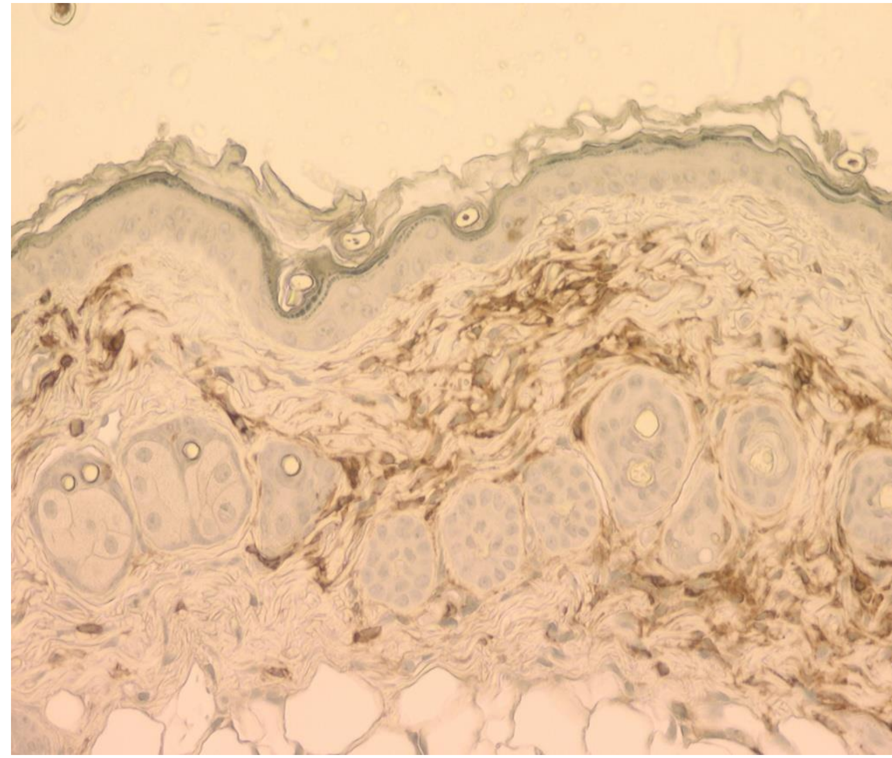


Survival Fractions EMT 6.5



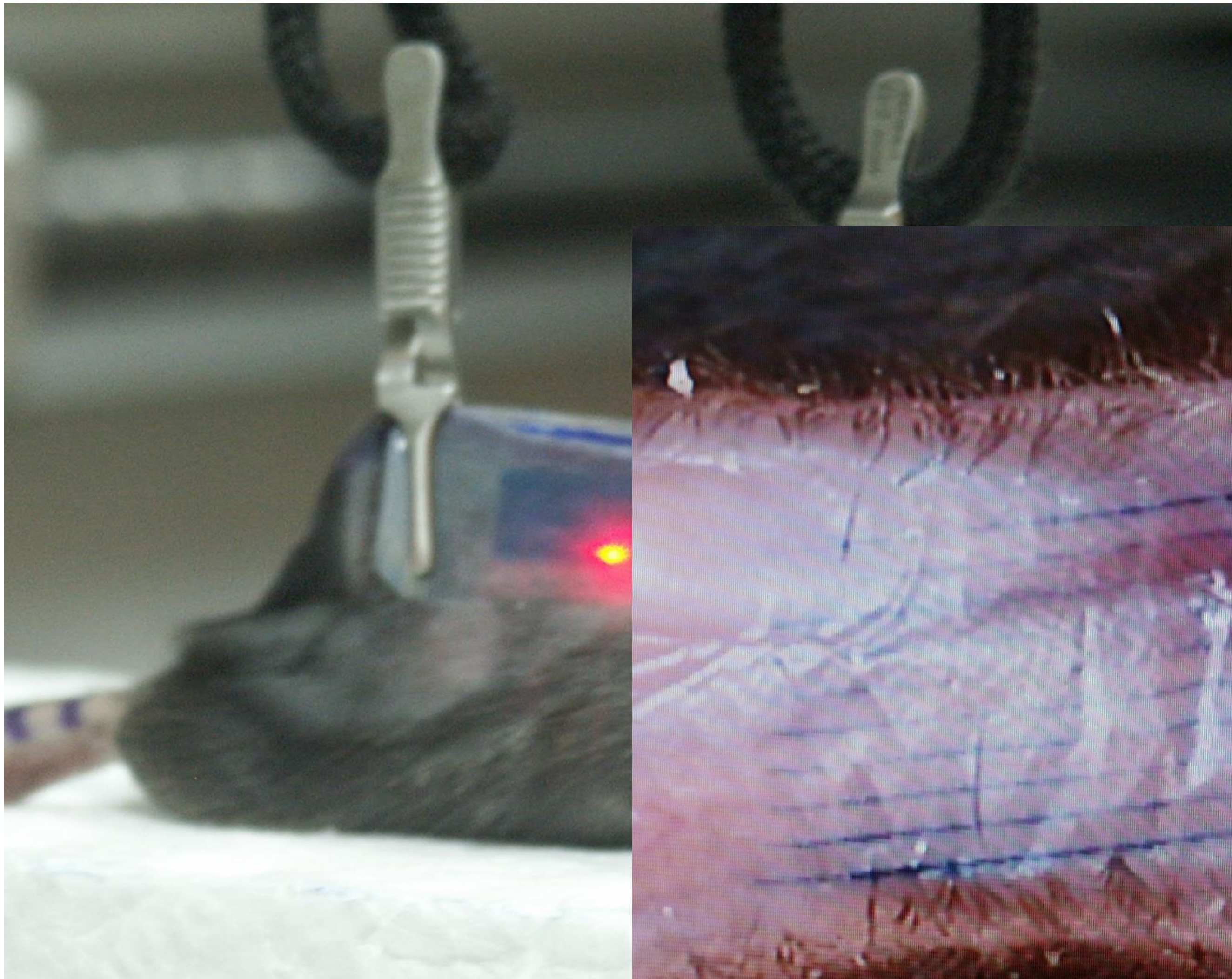
Results - Immunohistochemistry





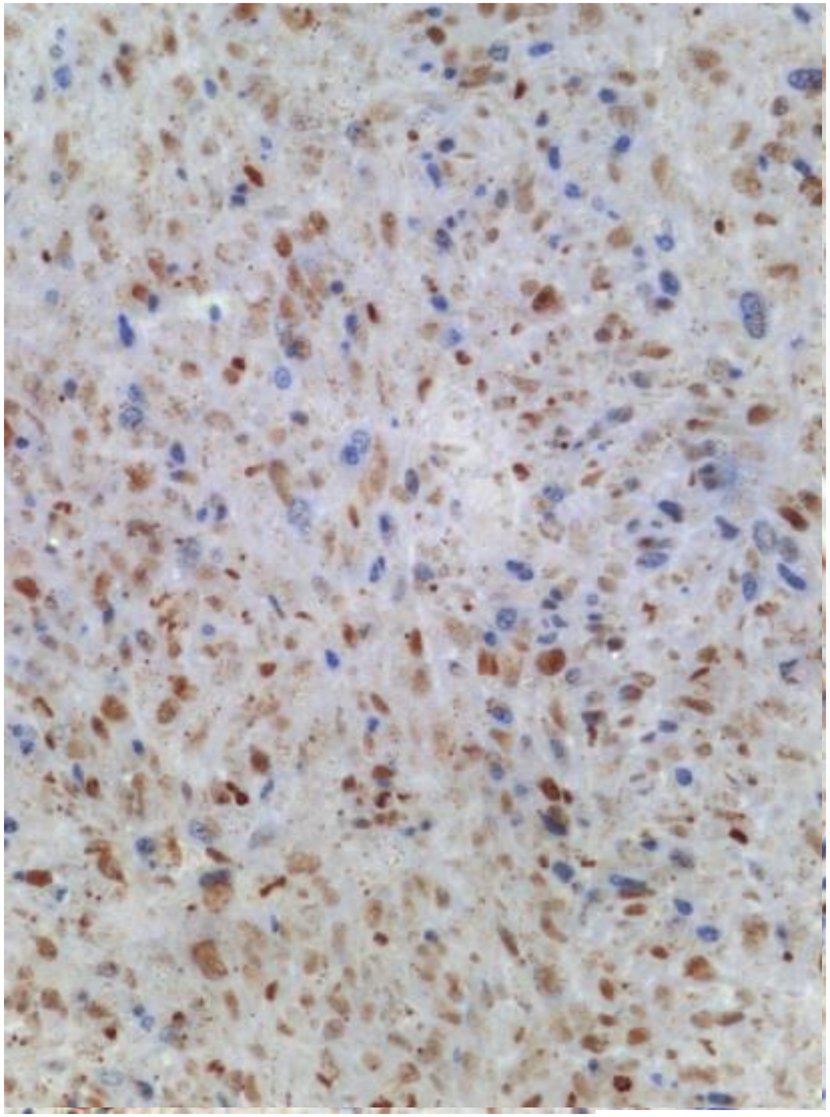
- H&E and CD45 Leukocyte Common Antigen (LCA) Staining of MRT-irradiated Mouse skin 5.5 days PI (x 100)
- Intact hair follicles & sebaceous glands

Using Radiochromic Film to Locate Microbeams

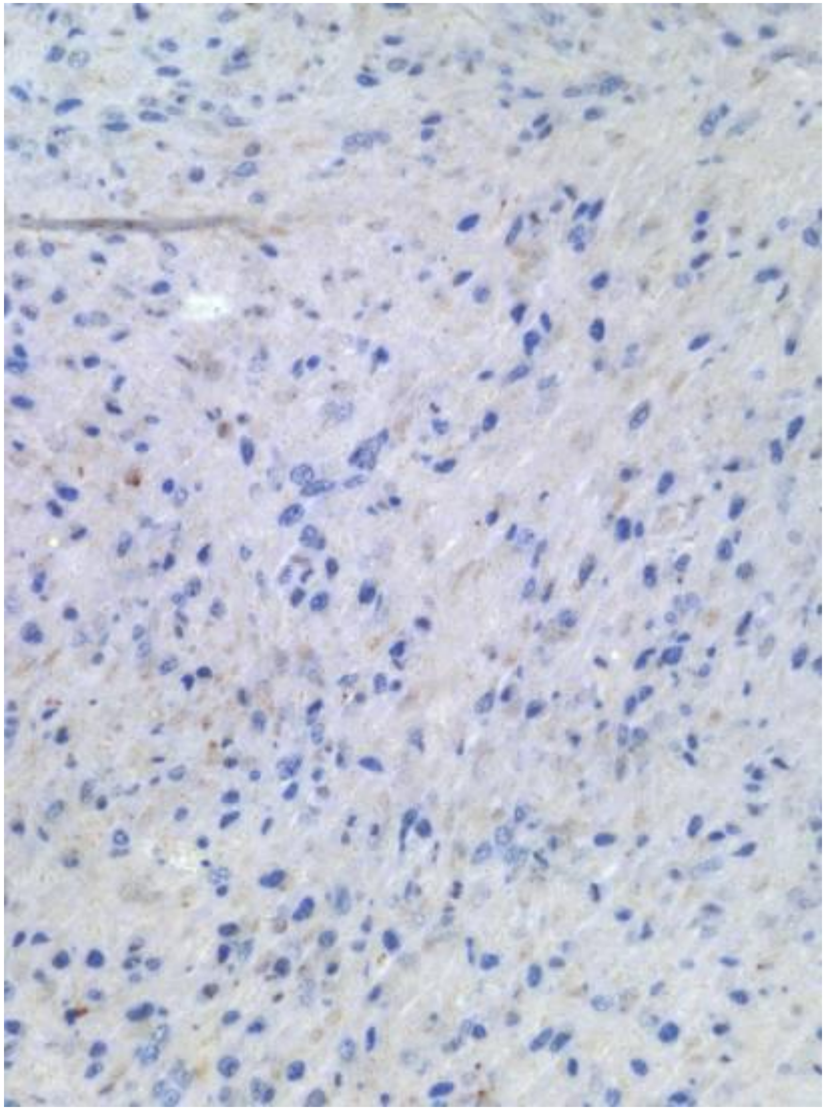


γH2AX/BrdU IHC post 560 Gy

MRT treated



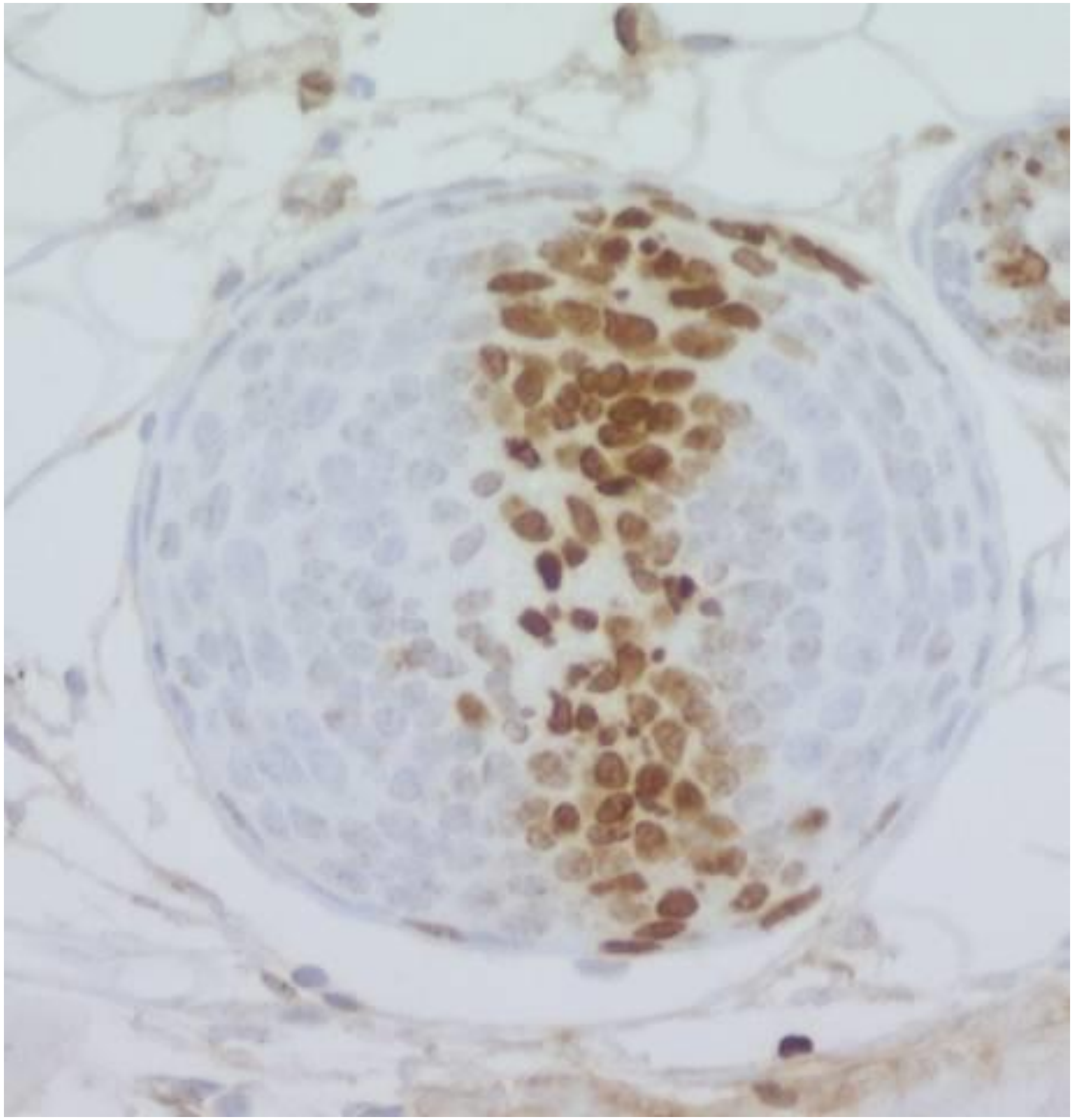
Control



48 hours after irradiation

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

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- Naoto Yagi
- Kentaro Uesugi
- Kaye Morgan
- Sally Irvine
- David Parsons
- Peter Rogers
- Jeff Crosbie